PLAINTIFFS' MEMORANDUM OF LAW IN OPPOSITION TO
DEFENDANTS' MOTION FOR SUMMARY JUDGMENT RE NUISANCE

EXHIBIT 14

FILED UNDER SEAL

EXPERT REPORT OF KATHERINE KEYES, PHD

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I. BACKGROUND AND QUALIFICATIONS

A. Summary

I am an Associate Professor of Epidemiology at Columbia University, specializing in substance use and substance use disorders epidemiology.

B. Education

I received a Masters degree in Public Health from Columbia University in 2004, and a PhD in Epidemiology from Columbia University in 2010.

C. Field of specialty and employment history

My field of specialty is substance use and substance use disorders, as well as related comorbidity, focusing on psychiatric disorders, and consequences of substance use including intentional and unintentional injury. After receiving my PhD in Epidemiology in 2010, I completed a post-doctoral fellowship in Epidemiology at Columbia University from 2010 through 2012, and then was recruited by Columbia University to join the faculty in 2012 as a tenure-track Assistant Professor. I was promoted to Associate Professor in 2016, and received tenure at Columba University in 2020. I also hold academic appointments at various other universities. I am a Research Assistant Professor at the University of Michigan, and an Adjunct Associate Professor at the Society for Health and Research at Universidad Mayor in Santiago, Chile.

D. Research areas and publications

I have published 271 peer-reviewed articles, editorials, and book chapters, more than 70 of which are first-authored. Much of this research has been published in the leading, highest impact epidemiology, psychiatry, and substance use journals, including in *Pediatrics, JAMA Psychiatry, Lancet Psychiatry, Nature Communications, British Medical Journal, British Journal of Psychiatry, American Journal of Psychiatry, American Journal of Epidemiology,* and *International Journal of Epidemiology*, among others. My articles have been cited in numerous disciplines, including psychiatry, epidemiology, public health, and pediatrics. My *h*-index ranges from 74[*] on Google Scholar. Currently, 50 of my articles have been cited more than 100 times; 15 of my articles have been cited more than 200 times; and 4 have been cited more than 500 times. Since obtaining my doctoral degree, I have led and sustained numerous grant-funded projects as Principal Investigator, and have successfully competed for grant funding from the National Institutes of Health to conduct my research. I have received numerous grants from Columbia University for my work, including the Calderone Prize for junior faculty, and the Tow scholarship (awarded to high-achieving mid-career scientists). I serve as a co-Investigator on numerous federally-funded projects both at Columbia and at other institutions (including University of Michigan and New York University). In 2019, I was named as a "Highly Cited Researcher" by Web of Science, which recognizes "the world's most influential researchers of the past decade, demonstrated by the production of multiple highly-cited papers that rank in the top 1% by citations for the field and year in Web of Science."

I have published two textbooks on epidemiological methods, and I am well-qualified to assess the literature on opioid-related harm. The first is *Epidemiology Matters: A New Introduction to Methodological Foundations*, published by Oxford University Press in 2014, which is currently being used to teach graduate students about epidemiological methods in more than 20 universities. The second is *Population Health Science*, also published by Oxford University Press, which details the theoretical and methodological foundations of the science of public health.

[*] An *h*-index is a measure of productivity and research impact. It measures the correlation between the number of peer-reviewed papers and the number of times each paper. An *h*-index of 68 indicates that I have published a median of 68 papers that have been cited at least 68 times. Benchmarks for *h*-indices vary; at Columbia University the standards for promotion in the department of epidemiology, are an *h*-index of at least 15 for promotion to Associate Professor, and at least 25 for promotion to professor. My *h*-index is more than twice that needed for a full professor rank in my department at Columbia University, indicative of high productivity and impact.

My expertise on opioid-related harm includes large scale survey data and vital statistics analyses, as well as the development of theories, hypotheses, and publishing findings concerning the role of macro-social factors in producing opioid epidemics. Specifically, I have extensively used high-quality survey data collected at the national level in order to estimate incidence, prevalence, and trends in risk factors for opioid use disorders, and trends in opioid use. Further, I have utilized data on fatal and non-fatal overdose to estimate determinants of variation in overdose across communities. My work focuses on community-based sampling strategies as well as hospital records to document epidemiological correlates and determinants of risk. I have published 21 peer-reviewed journal articles on opioid use and related harms (and many more on drug use disorders more generally), detailing trends over time in prescription opioid misuse, birth cohort trends in nonmedical opioid use and overdose, risk factors for non-medical prescription opioid use, and consequences of use across developmental periods, including consequences related to overdose. I have particularly focused on elucidating drivers of population-level trends, including literature reviews, synthesis, and empirical analyses of urban-rural differences in nonmedical opioid use and overdose. This work is aided by the 2019 inauguration of the Policy and Health Initiatives on Opioids and Other Substances (PHIOS) center at Columbia University based in the department of epidemiology, where I serve as a faculty member and also as a steering committee member of the Substance Abuse Epidemiology Training Program (SAETP), by which I train and mentor doctoral and post-doctoral scholars in substance abuse epidemiology. I am an investigator on the HEALing Communities Study, a large, $350 million dollar NIH-funded initiative aiming to reduce opioid overdose by 40 percent in four states, including New York, Ohio, Kentucky, and Massachusetts through implementation and dissemination of evidence-based prevention and intervention efforts, including expanded access to medication for opioid use disorder, distribution of naloxone to reverse overdose, and efforts to reduce high-risk prescribing. My role on the project is to develop mathematical simulations of the cycle of opioid use in New York State, and to estimate the anticipated reduction in overdose deaths by simulating combinations of intervention initiatives taking into account the system dynamics of counties in New York State. I am also a co-investigator of an NIH grant-funded project focused on estimating the impact of policies that target opioid use (e.g., prescription drug monitoring programs, prescribing and clinic laws, Good Samaritan laws, etc.) on opioid and benzodiazepine co-prescribing and overdose. Thus, I am well-qualified to review the literature and offer opinions based on the evidence and my own experience. I have no conflicts of interest in making these assessments, and have never consulted on behalf of any entities that stand to profit from drug or medical device sales.

E. Professional Organizations/Professional Societies/Awards

I have assumed national and international leadership roles in my areas of expertise. I am currently on the executive board of the *Society for Epidemiological Research*, to which I was elected by my peers. I am on the executive board of the *World Psychiatric Association Epidemiology and Public Health* section, and, in 2018, hosted the bi-annual meeting of the section at Columbia University. I serve on committees and boards for numerous other societies, including the *Research Society on Alcoholism* (program committee), *International Association of Population Health Science* (program committee), and *Society for Research on Adolescents* (dissertation award committee) among others, and each year I actively participate as a symposium chair and speaker on multiple workshops and roundtables at each of these meetings. In 2017, I was invited to join a National Academies of Sciences committee on accelerating the progress to reduce alcohol-impaired driving and contributed to the consensus report with evidence-based policy recommendations.[1] I have served on numerous NIH review committees for several study sections and institutes, and I joined the Epidemiology, Prevention and Behavior Research Review subcommittee of the National Institute of Alcohol Abuse and Alcoholism in 2019. Finally, I serve as Associate Editor of the journal *Drug and Alcohol Dependence* and as field editor for *Alcoholism: Clinical and Experimental Research*, both of which are highly regarded journals for original research on alcohol and drug use disorders and related harms.

My career achievements have been recognized with numerous awards. I was given the early career achievement award by three scientific societies (*Research Society on Alcoholism, American Psychopathological Association,* and *the World Psychiatric Association Epidemiology and Public Health Section*), as well as the *NIH Office of Disease Prevention Early-Stage Investigator* award, a competitive award recognizing two scholars per year, from any

NIH institute, who are poised to become leaders in the field. I have been and continue to be invited as a speaker nationally and internationally, with approximately 40 invited lectures, including 22 between 2017 and 2019.

II. OPINIONS

For the detailed reasons stated in this report, I intend to offer the following opinions in this case:

1. Medical use of opioids is associated with the development of opioid use disorder at higher rates than were reported by drug manufacturers. This assessment is based on standard principles and methods in the field of epidemiology, including confounding assessments, as well as consistency with biological knowledge, replication, dose response and length of opioid use among medical users.

2. Opioid use disorder is prevalent and disabling and occurs in approximately 8-12% of medical users; this estimate is likely an underestimate given that systematic assessment are not routinely done, and that tolerance and withdrawal after medical prescription cannot be diagnosed as opioid use disorder as of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), a change that was industry-supported and relies on no statistical evidence of which I am aware.

3. The opioid supply increased dramatically in the United States beginning in the mid 1990s, and a direct consequence of the increased supply of opioids was an increase in the incidence and prevalence of opioid use disorder among both medical patients and non-patients (among non-patients, over-supply of opioids were diverted to illicit marketplaces).

4. The epidemic of opioid-related harm began with a rapid increase in prescription opioid overdose death; prescription opioids were identified as the primary opioid contributing to overdose mortality in the early years of the epidemiology (late 1990s and early 2000s); the epidemic then transitioned to heroin use being identified more frequently in opioid overdose deaths (while prescription opioids remained high), and since approximately 2013, synthetic opioids (primarily fentanyl) have been increasingly identified in opioid deaths. Fentanyl deaths did not increase uniformly in all locations; data from Cabell County indicate that fentanyl mortality began increasing after 2014. The expansion of prescription opioid distribution and availability laid the foundation for the increase in heroin and fentanyl deaths, and my report details the existing literature on the extensive evidence that prescription opioids modally precede heroin and fentanyl use, providing a basis for the opinion that prescription opioid use is a cause of subsequent heroin and fentanyl use, morbidity, and mortality.

5. The expansion of non-medical prescription opioid use would not have occurred without the widespread availability of prescription opioids that were originally dispensed supposedly (but not always actually) for medical uses, often in greater quantities and doses than needed, leaving a surplus of opioids that could be diverted for non-medical uses.

6. Prescription opioid use is causally associated with harm across the lifecourse, especially when it is initiated at critical developmental windows such as adolescence, and during fetal development due to maternal use.

7. Prescription opioid use is causally related to subsequent heroin use. Approximately 70-80% of individuals who began using heroin in the last two decades used prescription opioids before heroin, and while the proportion of prescription opioid users who progress to heroin use is relatively small, even small increases in the proportion who progress can explain the majority of increases in heroin use in the United States. Because the heroin supply has been contaminated with high-potency synthetic opioids (e.g., fentanyl) since approximately 2013, prescription opioid use is also causally related to the increase in synthetic opioid morbidity and mortality, since prescription opioids frequently precede the transition to heroin, including heroin contaminated with fentanyl.

8. Prescription opioid overdose increased exponentially in the United States in the past 20 years, and these increases strongly correlate with rates of prescription opioid supply for medical use both in

terms of geographic variation in supply as well as year-to-year variation, in both observational and quasi-experimental studies, providing an evidence base that supports this opinion that supply and availability of opioids caused an increase in the rate of prescription opioid overdose.

9. Prescription opioids cause accelerated and increased risk of harm when used in conjunction with other drugs such as other opioids, benzodiazepines, stimulants, and alcohol. When multiple drugs are listed as part of the contributing causes of death in an overdose death, the preponderance of evidence indicates that certain combinations of drugs, especially those that include opioids, are associated with multiplicative increases in risk of death; that is, without the prescription opioid, the individual would not have died when and how they did. Thus, multiple drugs present in a toxicology report are likely indicative of drug-drug interactions for which prescription opioids are attributed as a cause when listed as per the current available evidence in epidemiological and toxicological sciences. For these reasons, CDC and other authoritative sources correctly report overdose deaths that include prescription opioids as prescription-opioid deaths, even when additional drugs are identified.[2]

10. In the United States, almost 47,000 people in the US died of a drug overdose in 2018 for an opioid-involved overdose death rate of 14.6 per 100,000,[3] an almost 6-fold increase since 1999.[4–6] The beginning of the opioid crisis was marked by a rise in prescription opioid overdose deaths. West Virginia has the highest rate of opioid overdose in the nation, and among counties that report overdose rates, Cabell County has been among top ten counties with the highest overdose rate for the last four out of four years. In 2018, the last year of data available, I estimate that the prevalence of extra-medical opioid use is approximately 8-9% in the general population, underlying more than 100 people who have died due to opioid overdose. Approximately three quarters of those who use extra-medically, and those fatally injured by opioids, began their opioid use with prescription opioids.

11. In addition to fatal overdose, other consequences to the Cabell Huntington community affected by opioid oversupply include emergency department visits for overdose, increased burden in the treatment and chemical dependency provider system, opioid use disorder and opioid use among both adults and adolescents, and neonatal abstinence syndrome (NAS).

12. Prescription opioid and other opioid mortality disproportionately affected economically deprived areas; however, the available evidence indicates that economic conditions played a relatively small part in increased opioid-related morbidity and mortality. The driving force in increasing opioid-related morbidity and mortality was, and continues to be, access to and wide-spread availability of opioids.

13. Compared with other commonly used pain relievers, such as non-steroidal anti-inflammatory drugs (NSAIDs), the adverse health and addiction consequences are substantially and significantly greater from opioids than from NSAIDs, including for cardiovascular events, fractures, and falls, as well as poisoning and overdose.

To summarize, there is compelling evidence of harm from the oversupply of prescription opioids, both for medical users, and to non-medical users because of diversion. The Cabell Huntington community has experienced a high burden of harm due to opioids. These harms include opioid use disorders and overdose; these harms are greater than those associated with other pain relief drugs, and are causally related to additional harms from opioids including transition to heroin addiction.

III. METHODOLOGY

A. Definitions of methodological and substantive terms

Before detailing the scientific evidence that underlies my opinions, it is useful to describe a set of terms that I will be using throughout the report.

1. *The Cabell Huntington Community.* Throughout this report I will be describing epidemiological trends that relate to the county of Cabell in West Virginia, as well as the City of Huntington. I will note

specifically where data that are referred to are drawn from, but the inference for the report should be understood to relate to the overall community that is included in Cabell County and the City of Huntington.

2. *Prescription opioids*. Drugs approved for medical use in the United States for the control of moderate to severe pain that are either natural opiate analgesics derived from opium (morphine and codeine), semi-synthetic opioid analgesics (oxycodone, hydrocodone, hydromorphone, and oxymorphone), synthetic opioids (methadone), or synthetic opioid analgesics (e.g., tramadol and fentanyl).[7]

3. *Medical use of prescription opioids*. Medical use will refer to use of prescription opioids prescribed by a physician and used as directed by that physician exercising professional judgment acting within the scope of his or her license.

4. *Non-medical use of prescription opioids*. Non-medical use refers to both using prescription opioids more often or longer than prescribed, or use of prescription opioids without a prescription. These definitions are commonly used in large scale surveys of prescription opioid use in the population. For example, the National Survey on Drug Use and Health asks, "Have you ever, even once, used any prescription pain reliever in any way a doctor did not direct you to use it?" Examples given to respondents include use without a prescription, use in greater amounts, more often, or longer than prescribed, or use in any other way that a doctor did not direct. This question and similarly worded questions on other large-scale surveys are the commonly used assessment of non-medical prescription opioid use. Some reports also label this as "prescription opioid misuse"; however, I will use the term 'non-medical prescription opioid use' for consistency. Non-medical prescription opioid use is also referred to as *'opioid misuse'* in much of the literature, although definitions and measurement assessments differ in what is included as opioid misuse. For example, some measures of opioid misuse include using opioids for euphoria, or for the experience or feeling that using opioids caused, which could conflate some medical and non-medical reasons for use.[8]

5. *Opioid misuse*. For the purposes of this report, opioid misuse is synonymous with "non-medical prescription opioid use", and refers to use of prescription opioids in ways other than prescribed, including taking more than prescribed, or using prescription opioids that were not prescribed by a physician. As noted above, however, throughout this report I will detail the definitions that studies use when using the term "misuse" to highlight variation in the definition in the literature, and will primarily rely on the term "non-medical use of prescription opioids" when discussing the literature and findings related to use of opioids that is outside the medical oversight and prescription of a physician.

6. *Tolerance and physical opioid dependence*. Individuals who use opioids can develop tolerance to the medication. Tolerance develops when the endogenous opioid system acclimates to the medication and more is needed to produce the desired effects. Dependence on opioids also occurs in medical uses of opioids, in which more opioids are needed to achieve the desired effects (tolerance) and when the cessation of opioids produces symptoms of withdrawal and craving for opioids. Physical opioid dependence can occur even at low doses, but is increased with dose and duration of use. Physical opioid dependence does not currently meet the criteria for opioid use disorder, with changes to the DSM in the most recent revision. Physical opioid dependence is expected even when opioids are used medically; yet physical opioid dependence is clinically challenging, and increases the risk for transition of patients to opioid use disorders and addiction.

7. *Opioid use disorders*. Opioid use disorder is a diagnosis in the DSM, as well as the International Classification of Disease (ICD). It is important to point out from the outset of this description that opioid use disorder is distinct from the physical opioid dependence (defined above) that would be expected to occur with repeated administration of opioids. Medical use of opioids would be expected to produce symptoms such as tolerance (needing more opioids to achieve the same effect) and withdrawal (uncomfortable and painful physical and psychological symptoms during cessation of opioids). However, opioid use disorders involve a maladaptive pattern of use from which there are serious consequences in domains of functioning. The fourth version of the DSM was published in 1994, and included two diagnoses that together comprised opioid use disorders: opioid abuse and opioid dependence. Opioid abuse was diagnosed if there was "a maladaptive pattern of use leading to clinically significant distress or impairment" as indexed by at least one of four symptoms in a 12-month period, including recurrent failure to fulfill major role obligations (e.g.,

repeated absences from work, neglect of children), recurrent use in physically hazardous situations (e.g., driving under the influence), continued use despite social or interpersonal problems because of use (e.g., arguments with family, physical fights while intoxicated), and legal problems due to use.[9] Opioid dependence was diagnosed if there was "a maladaptive pattern of use leading to clinically significant distress or impairment" as indexed by at least three of seven symptoms in a 12-month period including tolerance (needing more opioids to achieve intoxication or desire effect, or diminished effect with continued use of the same amount of opioids), withdrawal (defined via a substance specific syndrome), using the substance in larger amounts or over a longer period than intended, persistent desire or unsuccessful efforts to cut down or control use, physical or emotional problems caused or exacerbated by use, excessive time spent in activities to obtain or use substance, and social/occupational/recreational activities given up in order to use.[9] Tolerance and withdrawal are symptoms of opioid use disorder; tolerance and withdrawal alone were excluded as a sole set of criteria for OUD diagnosis in DSM-5. This change to exclude individuals from diagnosis when based on tolerance and withdrawal alone underestimates the total burden of opioid use disorder in the population, given that psychometric and epidemiological evidence indicates that tolerance and withdrawal are valid indicators on the dimension of opioid use disorder (discussed further on Page 20 of this report). In DSM-IV, opioid abuse could only be diagnosed if the criteria for opioid dependence were not met. In DSM-5, opioid abuse and dependence criteria were combined for a single diagnosis of "opioid use disorder"; craving was added as a criterion (strong desires to use opioids); and "legal problems" was removed as a criterion. Diagnoses could be made at three levels: mild (2-3 symptoms); moderate (4-5 symptoms); and severe (6+ symptoms). Opioid use disorder diagnoses are sometimes made based on ICD-9 and ICD-10 criteria. These criteria overlap substantially with DSM criteria

8. *Addiction.* Addiction is a concept often synonymous with opioid use disorder, but is not a clinical term available for diagnosis in major nosology such as the DSM or the ICD. However, it is used frequently in the literature with various definitions, sometimes used to refer to physical opioid dependence, but most often to refer to individuals who use opioids non-medically for their euphoric effect, and/or those who exhibit harms due to opioids that include important social, occupational, physical, and relationship impairments due to non-medical prescription opioid use. Because addiction is not a well-defined clinical diagnosis, throughout this report I will detail how "addiction" is defined in studies that use the term, and will focus on opioid use disorder primarily when discussing the literature on opioid-related harms.

9. *Overdose.* An injury to the body caused by poisoning from excessive opioid use. Symptoms of an overdose include shallow breathing, weak pulse, loss of consciousness, and constricted pupils. An overdose can be fatal or non-fatal.

10. *Incidence.* Incidence, or incidence rates, refers to new diagnosis over a population at risk for developing the outcome during a specified time interval or per a specified time scale. For example, the incidence of opioid use disorder would be an assessment of newly developed cases among those who did not previously have a diagnosis across a specified time interval.

11. *Prevalence.* Prevalence, or prevalence rates, refers to the total number of cases over a well-described population. For example, the prevalence of opioid use disorder in a given year would be estimated as the total number of cases of opioid use disorder (both new and persistent) over the total population size.

12. *Relationship between incidence and prevalence.* Prevalence and incidence are both used to demonstrate total burden of harm for health outcomes in the United States. Prevalence rates provide essential information regarding the counts of cases and are a combination of new and existing over time, and can be used to assess risk factors and correlations. Because prevalence includes both new and existing cases, the prevalence of an outcome in a given population at a given time is estimated by the incidence rate multiplied by the average duration of the outcome (given a steady state population). Prevalence is critical for determining total burden of health outcomes, especially to assess surveillance of trends over time. Incidence of an outcome is critical for documenting emerging epidemics and the existence of new cases. The assessment of risk factors for incident cases is of interest because it can establish the extent to which exposures generate new cases of a health outcome; risk factors for prevalent cases combine risk factors for

new cases plus risk factors for cases that are chronic or un-resolving. This report will include information on both incidence and prevalence.

13. *Diversion*. Diversion of opioids has been defined in various ways across a variety of sources, including the transfer of opioids obtained through legal medical sources to the illicit marketplace. I will use a broader definition of diversion, which is consistent with numerous other scholars, which is that diversion occurs when opioids are diverted from their intended recipient, for example, when traded for monetary value, barter, or for no cost among family and individuals in a shared social network, or when sold for money by illicit dealers and traffickers. Opioids that are prescribed to individuals who knowingly deceive prescribers to obtain opioids, as well as by physicians who knowingly prescribe to individuals with no legitimate medical need, have a high likelihood of being diverted for non-medical use.

14. *Morbidity*. Morbidity refers to specific health conditions. In the context of this report, morbidity refers to conditions subsequent to opioid use such as opioid use disorder, non-fatal overdose and hospitalization, and other acute and chronic health conditions that arise from opioid use.

15. *Comorbidity*. Comorbidity refers to two or more specific health conditions of interest occurring concurrently. For example, individuals who have more than one drug use disorder simultaneously have comorbid drug use disorders.

16. *Systematic review*. A systematic review is designed to carefully summarize existing evidence on a specific topic. Systematic reviews provide defined search criteria in the peer-reviewed literature, report articles that were included an excluded with transparent criteria, and the relevancy of the studies included for generating conclusions about the research question under consideration. Judgments are made from systematic reviews about the quality of evidence that has been gathered, existing gaps in the research, and quantitative as well as qualitative assessments of the strength of the evidence. The purpose of a systematic review is to summarize the strength of the evidence for a particular topic. However, systematic reviews can be well or poorly executed, and their utility and reliability needs to be assessed carefully just like any other peer-reviewed publication.

17. *Meta-analysis*. Meta-analysis quantitatively combines evidence across studies to provide summary estimates for the association between exposures and outcomes. Meta-analyses take published and in some cases unpublished estimates from across studies and uses them to generate a summary estimate with more statistical power because of the combined effect across studies. Methods in meta-analysis allow researchers to weight studies based on quality or informativeness, such that studies that have a higher quality of evidence can be given a greater weight in determining the summary estimate. Meta-analyses are considered a higher level of evidence than single studies, because while single studies may have particular bias or confounding, a large number of studies analyzed together generally provide a more rigorous estimate of the true relationship. Studies that are included in a meta-analysis should be sufficiently similar to warrant summarizing estimates of magnitudes of association together, while simultaneously estimating heterogeneity in effect sizes across studies. As in the case of systematic reviews, meta-analyses can be well or poorly executed, and their utility and reliability needs to be assessed carefully just like any other peer-reviewed publication.

18. *Confounding*. Confounding occurs when risk factors that are causes of the outcome are unequally distributed between exposed and unexposed persons. Study estimates that are confounded do not reflect the true causal relationship between exposures and outcomes. For example, consider the relationship between prescription opioid use (exposure) and heroin use (outcome), which is evaluated in this report. Men are more likely to both use prescription opioids and to use heroin. Thus, the estimate of the relationship between prescription opioid use and heroin use is confounded by sex, and control for sex in statistical analyses of the relationship would be appropriate.

19. *Bias and misclassification*. Bias can arise in the study design and analysis of epidemiological studies from a variety of sources. Among the most pernicious forms of bias in epidemiological studies is information bias, also called misclassification. For example, a common source of misclassification in studies

of substance use disorder occurs when reporting on the presence of substance use disorder among a group of research subjects, any substance use disorder that is missed among research subjects would be characterized as misclassification. With regard to opioid use disorders, the presence of disorder is often underestimated due to misclassification of opioid dependent individuals as non-dependent. Misclassification is magnified when opioid use disorders are not assessed with structured, validated instruments for measurement of opioid use disorder, or with objective assessments of the presence of opioids and other drugs through urine toxicology. Further, misclassification has been assessed in vital statistics designations of causes of death for which opioids may be involved.[10] Death certificate procedures vary by state and local region within state, in terms of the training of the individual completing and certifying the death certificate, and with regard to the quality and completeness of the information presented on the death certificate. However, it is worth noting that the high-quality procedures conducted to investigate and designate overdose deaths in West Virginia have been documented. Drug overdose death data have been reviewed and maintained by the West Virginia Department of Health and Human Resources Bureau for Public Health along with the Office of the Chief Medical Examiner with examination of toxicology results and investigations as reported on death certificates since at least 2001.[11] Further, as outlined in reports and peer-reviewed publications,[11–13] the West Virginia Office of the Chief Medical Examiner created a forensic drug database in 2005 to track and record information on overdose. Overdose deaths are designated based on forensic investigation and pathology, including toxicology and autopsy, preceded by drug screening which is conducted in all medical examiner-referred deaths. Toxicology is then confirmed through tissue sampling with high-quality and high-validity tests for the presence of a wide range of opioids. Thus, data on overdose from West Virginia is of high quality.

B. What role does epidemiology play in describing opioid-related harm?

Epidemiology is the "science of understanding the causes and distributions of population health."[14] To understand causes and distributions, epidemiologists examine the dynamic nature of populations and how health and disease arise within them, as well as the conditions that shape population health over time and space, including policies, practices, and politics that create conditions that improve or deteriorate population health. Whereas a physician examines each patient that enters her clinic, asking what caused a particular health outcome for this particular patient, an epidemiologist looks over the landscape of a population across time to determine why the burden of a particular health outcome is greater or worse in some areas, at some time points, and among some subgroups, and queries what in the social, political, and environmental landscape create the distributions and their changes over time.

Epidemiology has played a key role in understanding the increases in opioid use and related harm in the population. A central role for epidemiology is surveillance. Using a variety of methods, epidemiologists examine the incidence and prevalence of opioid use, non-medical opioid use, and consequences of use such as opioid use disorders, overdose, and neo-natal abstinence syndrome across time and place, as well as factors that influence opioid prescribing, use, and misuse. Epidemiological studies have documented changes in the incidence and prevalence of these outcomes across time, heterogeneity in the incidence and prevalence by state and county, and correlations with factors such as availability and access of opioids, individual-level risk factors, and policy changes. Further, epidemiological studies are critical in documenting the longitudinal short- and long-term consequences of inter-individual variation in risks associated with opioid use. That is, epidemiological studies compare individuals with and without specific opioid use patterns to determine the longitudinal associations between use and health and mortality. Epidemiologists are particularly trained to control for and examine confounding, which is commonly used to mean common causes of an exposure and an outcome that are being assessed. When confounding is present, groups are not comparable to each other on causes of the outcomes other than exposure. For example, individuals who do and do not use opioids (both medically and non-medically) may have different underlying risk factors for long-term health and mortality risks, and thus the science of epidemiology involves testing the extent to which relationships between exposures and outcomes are robust to statistical controls for these risk factors. Epidemiologists use a variety of methods to control for confounding in estimates, including statistical controls in regression models, propensity scores estimation, randomization, and quasi-experimental methods such as instrumental variable analysis. In summary, the role of epidemiology in describing opioids is to quantify the extent to which use and

harms associated with use are changing over time, the determinants of those changes, as well as individual-level risk factors for non-medical use and harm.

Key to epidemiological assessments is the concept of risk factors. Risk factors are variables that, when present, increase the frequency with which an outcome occurs, but need not be necessary or sufficient for the occurrence of the outcome to be fully determined. A useful example is that of cigarette smoking and lung cancer. It is now widely accepted that cigarette smoking is a cause of lung cancer. However, not all cigarette smokers will develop lung cancer (thus, cigarette smoking is not sufficient to cause lung cancer in and of itself), and not all lung cancers occur among smokers (thus, cigarette smoking is not fully necessary to cause lung cancer). Yet, cigarette smoking increases the risk that lung cancer will occur, and thus it is considered a cause of lung cancer if there are cases of lung cancer that would not have occurred in the absence of cigarette smoking. I will apply the same "risk factor" framework to my assessment of the causes of the opioid crisis, considering factors to be causes of opioid use disorders, overdose, and related harm if some cases would not have occurred in the absence of prescription opioid use. This framework does not preclude or ignore that addiction and related harms are multi-factorial in their etiology, but rather asks whether there are cases for which the outcome would not have occurred without the presence of prescription opioid use.

C. Methodology for review of the evidence

I undertook a review of the evidence to assess the impact of opioid sales and distribution in the United States, as well as harms incurred from opioid use, opioid use disorders, diversion, and transition to heroin on opioid-related outcomes and among families and children. I also estimate unmet need for treatment in the Cabell Huntington Community.

1. Literature search methodology

My review of the evidence began with a literature search. In order to conduct this literature search. I relied on methodology that is considered standard in the scientific process, as outlined below.

First, I used search terms in the peer-reviewed literature related to the areas of my literature search. For this I used PubMed (https://www.ncbi.nlm.nih.gov/pubmed/), a search engine produced and maintained by the US National Library of Medicine National Institutes of Health. Full texts of scientific articles produced in the searches were available by subscription through my faculty appointment at Columbia University. Search terms were entered into the search bar, and titles were then reviewed for relevance to each particular topic. Full- texts were then reviewed to determine if there was original data and information within each specific category that related to topics covered in the expert report. Full-text articles in journals that are indexed in PubMed are considered to be reputable; journals that are indexed by PubMed have long histories of publication, and are included only if they meet well-recognized standards including editorial oversight by recognized experts in the field as well as peer-review by experts.

Peer-review is considered to be the gold-standard of the scientific process; peers are experts in the field who evaluate each submitted paper for flaws in design and logic and make quality assessments. However, while peer-review is an important component of the scientific process, peer-review is not sufficient alone to establish quality and validity of a scientific study. Limitations in the peer-review system have long been documented in the scientific literature, including that inadequate study design and statistical analysis flaws go unnoticed by peer-reviewers,[15] publication biases lead to scientific studies with statistically significant results more likely to be published and cited than studies with null results,[16] incorrect and inaccurate reporting of study outcomes and results,[17] and the pernicious influence of conflicts of interest among study researchers that leads to bias in the conduct and reporting of research.[18] For example, the British Medical Journal found that financial ties of study investigators were associated with a 3-fold increase in positive study results, based on analysis of 190 clinical trials that were published in 2013.[19] While the scientific literature has made advances in the peer-review system through rigorous development of reporting guidelines, more clarity and specificity in the reporting of conflicts of interest, and the inclusion and compensation of editors who additionally review papers for quality, peer-reviewed studies should still be rigorously evaluated when deciding whether to cite them for a particular piece of evidence. In this report I have included studies assessed by peer-

review and done additional review of the articles based on my own expertise in order to discern whether they meet quality benchmarks. As an associate editor for multiple scientific journals, I have over a decade of experience evaluating the quality of the scientific literature for publication. I have served as a peer reviewer for hundreds of scientific papers in the field of substance use and substance use disorder epidemiology, and I am thus well qualified to evaluate the literature for papers that demonstrate a sufficient level of quality to be relied upon in my review of the evidence.

Second, within full-text reviews, additional studies that were relevant to each topic were identified based on the reference lists and citations of articles identified by PubMed search. Reference lists were reviewed and additional articles extracted based first on title review for broad relevance to the topic of study. Then, full texts were studied and evaluated, and included in the evidence review if the article contained original information that was reliable and relevant to the topic under study.

Finally, I also studied and evaluated the non-peer-reviewed "gray" literature relevant to the topics under study. Specifically, I reviewed government and agency reports from the following: Centers for Disease Control and Prevention, Substance Abuse and Mental Health Services Administration, and Agency for Healthcare Research and Quality. These reports included assessments of time trends in opioid poisoning and overdose, rates of opioid use disorder, and hospitalizations for opioid-related causes. Other gray literature was included in my evidence review based on review of reference lists from PubMed searches when relevant to the topic of study. I have also, where appropriate, considered new and novel data contained in Letters published in top tier journal where submissions are peer reviewed. I also considered materials provided by the Plaintiff's counsel, and they are included in the materials considered list.

2. Levels of evidence evaluated

Throughout this report, I make assessments of the rigor of the evidence that has been used to support conclusions and opinions. There are two general categories of studies that I will include in this report: the first are studies that examine associations, and the second are studies that examine trends over time.

With regard to studies that examine associations, I considered the following levels of evidence. First, I considered randomized controlled trials to be a high level of evidence, given that the possibility of confounding and bias to influence the results is most likely to be mitigated in randomized controlled trials. For example, in sections on evidence for opioid use disorder after medical use of opioids, I included randomized controlled trials that included information on outcomes such as 'aberrant drug use behavior'. However, for many of the associations reported in this statement, randomized controlled trials are unfeasible or unethical, or uninformative for the question of interest. For example when assessing the transition from prescription opioid to heroin use, it is highly unethical and would never be considered to randomize individuals to high levels of prescription opioids in order to observe the transition to heroin once prescription opioids were tapered. Indeed, for much of the literature cited in this report, randomized controlled trials would never be conducted. Furthermore, randomized controlled trials are not *de facto* strong evidence, as publication bias, conflicts of interest, specifics of the study design, study population assessed, outcome measurement, study duration, statistical power, and rigor of statistical analysis should all be considered when evaluating a particular randomized controlled trial for the level of evidence that it brings to a particular study question. For example, many randomized trial of prescription opioids are uninformative for relevant questions of opioid use disorder incidence due to the lack of systematic measures of opioid use disorder and psychiatric diagnoses, exclusions from participation in trials among those with prior substance use disorders, and low dose/short duration of opioid exposure. In the circumstances that randomized controlled trials were not available, rigorous, or applicable to the question at hand (e.g., risk of opioid use disorders among those prescribed opioids), I considered meta-analysis and systematic reviews to be high levels of evidence, and cite them as well as discuss their findings when they are available. Systematic reviews and meta-analysis are considered high levels of evidence because they quantitatively and qualitatively assess the overall body of the literature and provide quality assessments that weight evidence, but are subject to limitations if not conducted rigorously and are not taken as strong evidence without careful review. I consider studies that had prospective follow-up of patients or participants, a well-described strategy for statistical control of confounders, and well-

designed comparison groups to be the next level of evidence. Prospective follow-up is an important study design because it reduces biases in epidemiological studies from retrospective reporting of symptoms or events. Further, statistical controls are necessary to overcome the potential for bias from confounding. Prospective studies often involve comparison groups (e.g., prescription opioid users and a comparison group of non-prescription opioid users). Study designs with comparison groups provide evidence regarding opioid-related harm that is over and above harm in patient and general population samples across varying levels of opioid exposure. Studies of patient populations without comparison groups, however, are also informative particularly for research questions germane to the prevalence of opioid use disorders and related harm among patients prescribed opioids (especially high doses in long duration), as well as questions related to the proportion of drug users who previously used prescription opioids. Well-designed studies of single populations without explicit comparison groups are thus also considered by me as relevant evidence for characterization of prescription opioid-related harms.

With regard to studies that assess trends over time, I considered three data sources to be the highest levels of evidence. First, I relied on death records that are collected and harmonized by the national vital statistics surveillance system. While death records can have misclassification of causes of death, they are considered by experts to be a reliable indicator of national and local burden of specific causes of death, especially when examining trends over time. Second, I relied on data sources with a national reputation for transparency in reliability and validity that assess hospitalization and other clinical records, such as large electronic health databases, as well as national studies such as the National Inpatient Sample. Again, while such records can include misclassification, data sources gathered from reputable organizations such as the Agency for Healthcare Research and Quality include reliability and validity assessments that allow the researcher using them to be able to draw conclusions based on the best available evidence. Third, I relied on survey data that is routinely collected in the general population of households in the United States over time. Surveys are essential parts of surveillance, given that many cases of substance use disorder do not come to clinical attention, and thus relying on clinically ascertained records can give a biased assessment of trends and burden in the population. Survey data source methodology involves clustered sampling so that samples are representative of the entire United States, and respondents are interviewed with validated instruments that are designed to elicit diagnoses and information with maximum accuracy in the survey context. Generally, I do not include surveys that are not representative of the population, as they are not strong evidence for an assessment of the total burden and trends over time.

IV. DETAILED DISCUSSION OF OPINIONS AND REASONS AND BASES FOR THEM

A. Distribution, sales, and marketing of opioids increased in the 1990s

There is voluminous evidence regarding the increased distribution, sales, and marketing of opioids beginning in the 1990s. This evidence is the subject of other expert reports, and I will not repeat all of that evidence here. Instead, I will summarize some points for context. Opioid pain relievers became an increasingly widely-used option starting in the mid 1990s, particularly for chronic non-cancer pain, a use that had rarely been seen previously. Estimates from the Automation of Reports and Consolidated Orders System (ARCOS), which tracks prescription distribution and sales, indicate that prescription opioids were dispensed at an estimated 96 mg per person in 1997, and increased to 700 mg per person by 2007 (greater than 600% increase).[20,21] In 1995, the year OxyContin entered the market, the number of opioid prescriptions filled in the United States increased by 7 million, and continued to increase over the next two decades before peaking in the fourth quarter of 2012 at 62 million prescriptions dispensed.[22,23] From 1997 to 2002, prescriptions for OxyContin for non-cancer pain increased from approximately 670,000 in 1997 to about 6.2 million in 2002.[24] The increase in opioid prescribing was driven by a multitude of factors, including direct marketing to physicians using data that underestimated opioid use disorder risks in patients, which I will detail in Section B. Evidence shows that pharmaceutical marketing of prescription drugs increases prescribers' likelihood of prescribing the marketed drug in the future.[25,26] That is also true for prescription opioids; as a result, increasing marketing of opioid drugs led to increased sales of the marketed drugs.[27–29]

As discussed in detail below, based on the available evidence, including multiple studies, the rapid increase in total opioid prescribing levels after the introduction of OxyContin in 1996 correlates with marketing of opioids to physicians which downplayed the risks of harms associated with prescribing, including opioid use disorder and overdose.

Evidence published in 2019 indicates that the number of opioid prescriptions filled has declined in recent years,[30] and yet the number of opioid prescriptions filled remains high—and significantly higher than it was in the mid-1990s. Data from outpatient prescribing records from IQVIA Xponent database, covering 59,400 pharmacies (representing 92% of retail prescriptions dispensed in the United States) reflects trends from 2006 through 2017 in milligrams of prescribed opioids, duration per prescription, high dosage prescription fills (defined as a dosage equal to or greater than 90 morphine milligram equivalents [MMEs] per day), prescriptions filled for 3 days or fewer and 30 days or longer, and extended-released/long-acting formulation prescriptions.[30] While there are overall declines in opioid prescribing, and high dose prescribing, the volume of opioids prescribed remains high and prescription length continues to increase. Opioid prescriptions per person in the total United States increased annually at an average rate of 6.9% per year until 2010, and decreased at an average rate of 3.8% per year from 2010 through 2015. In 2017, there remained a high level of opioid prescribing in the United States, with 191,218,266 prescriptions dispensed, leading authors to conclude that still in 2017 "pharmacies filled enough opioid prescriptions to theoretically provide every US resident with 5 mg of hydrocodone bitartrate every 4 hours around the clock for 3 weeks."[30] Hydrocodone bitartrate has several formulations, including hydrocodone bitartrate with acetaminophen commonly known as Vicodin. Focusing on West Virginia in particular, evidence indicates that from 2006 through 2010, the increase in MME per person was higher than the national average, with an annual percentage increase of 8.6% (nationally the average annual increase was 6.9%); from 2010-2015, MME per person in West Virginia decreased 2.4% (nationally, the average annual decrease was 3.8%, indicating a slower decrease in West Virginia compared to the United States average), and from 2016-2017, the average annual decrease was 15.1% (higher than the national average annual decrease of 10.7%).[30]

These dynamics over time are also apparent within the Cabell Huntington Community. Based on IQVIA data published by county by the CDC,[31] the opioid prescribing rate in Cabell County increased from 175.3 to 186.6 prescriptions per 100 persons from 2006 to 2011 (note, this indicates that there were more than one prescriptions for *every resident* of Cabell County in these years); thereafter, prescribing decreased although remains extraordinarily high, with the rate per 100 persons of 92.1 in the most recent year of data available, 2018. Again, this indicates that there is almost 1 prescription for an opioid for every person in Cabell County, still, in 2018.

B. Risks of opioid use disorder following medical use of prescription opioids follow a "dose-response" pattern

Early studies cited in marketing materials to physicians underestimated the addiction potential of prescription opioids, and included claims that risks of opioid use disorders are rare among those prescribed opioids. Much of the material provided to physicians on the risks of opioid use disorders after medical prescription of opioids, however, was based on studies that were inadequate epidemiologically, such as Porter and Jick (1980),[32] which did not examine risk of use disorder or dependence based on dose or length of use of opioids, and did not use validated or objective assessments of opioid use disorder. Further, the doses, conditions, and range of medications actually provided to patients often differed from what was cited in these studies. The lack of attention to the to the risk of opioid use disorder with increasing dose and duration of opioids is particularly appalling given that before, during, and after the time period in which opioid distribution rapidly accelerated, there was a literature base to draw on regarding the risks of opioid use disorder indicating substantially higher risk of disorder symptoms among those under medical care than reported by industry,[24,33] with variation in the reported rates of OUD based on condition, dose, and duration of opioid use.[34–37] From early research, the epidemiological science supported the opinion that OUD rates increased with dose and duration of opioid use.

For this report I reviewed six systematic reviews and/or meta-analyses that assessed opioid use disorder among medical users of opioids.

Vowles et al. (2015)[38] provides the most transparent and high-quality review of the evidence of opioid use disorder among patients prescribed opioids for chronic pain. Vowles et al. (2015), unlike other reviews, calculated estimates of prevalence of three outcomes: (1) misuse, described by Vowles et al. as using opioids contrary to directed or prescribed; (2) abuse, described as intentional use of opioids for euphoric effects; (3) addiction, described as continued use with experience of, or demonstrated potential for, harm. Among studies reviewed, 38 studies met inclusion criteria, which is more comprehensive than comparable reviews also discussed in this report. I will focus on those studies that estimate opioid "misuse" and opioid "addiction". Given that the measurement of opioid misuse includes criteria of opioid use disorder (use more than intended or prescribed; difficulties with responsibilities as to work, school, appointments, etc.), the most reasonable analysis of the Vowles study in relation to DSM-5 criteria is that Vowles' 8-12% "addiction" rate corresponds to moderate-to-severe OUD, and Vowles' 21-29% category of "misuse" includes the full spectrum of DSM-5 categories, from mild (defined as 2-3 criteria met), moderate (4-5 symptoms) to severe OUD (6+ criteria met).[39,40] These studies measured addiction with a range of assessment tools, including diagnostic interviews and urine toxicology. Given that a higher threshold was indicated for "addiction" versus "misuse", the disorders assessed as "addiction" in the Vowles et al. (2015) review generally correspond to opioid use disorders that range from moderate (5-7 symptoms) to severe (8+ symptoms). The highest rates of addiction in Vowles et al. (2015) were documented by Jamison et al. (2010),[41] a sample of over 600 patients that were taking long-term prescribed opioids for non-cancer pain. Individuals in the study completed a series of questionnaires to measure opioid misuse, including patient and provider questionnaires, as well as urine toxicology tests. Opioid use disorder assessments were based on patients scoring above cut-points on the self-reported scale, and in the case that patients were below the cut-off, criteria for opioid use disorder were also considered to be met if the patient scored above a cut-point on the physician-reported aberrant behavior scale and the urine toxicology was positive for an illicit substance or an additional opioid medication that was not prescribed. Individuals in the study had been using opioids for an average of 5-6 years; 34.1% of the sample had evidence of opioid use disorder, including 31% of men and 36.7% of women, indicating a high level of opioid use disorders when patients are assessed with validated instruments, as well as objective measures of the presence of opioids such as urine toxicology. The study with the lowest reported rate of opioid use disorder or "addiction" cited in Vowles et al. (2015) was Edlund et al. (2007),[42] based on estimates from a nationally-representative survey of over 9,000 individuals in the community. Authors used several questions that map on to DSM-IV criteria for opioid use disorder. They did not include all criteria, however, and thus the reported evidence is for symptoms of opioid use disorder. Among those who had received a prescription for an opioid, the prevalence of opioid use disorders symptoms was more than 10 times higher than those who had not, at an estimated 7.3%,[†] which is in line with other literature on the range of addiction estimates among medical users of opioids. Controlling for a range of confounders, Edlund et al. (2007) documented that those who used prescription opioids had 3.07 times higher risk of opioid misuse, and 6.11 times higher rates of "addiction". These risk ratios were higher than for other known risk factors for substance use disorders such as mental health diagnoses. Further, the risk of "non-opioid illegal drug use" was not higher among prescription opioid users, suggesting specificity in the relationship between prescription opioid use, and subsequent opioid-related harms. It is important to note, however, that assessments of opioid use disorder based on questionnaires may be an underestimate due to patient reluctance to admit non-medical or aberrant drug use, and that urine toxicology may also be an underestimate because non-medical or aberrant use of prescribed opioid medications may not appear as aberrant on a urine toxicology.

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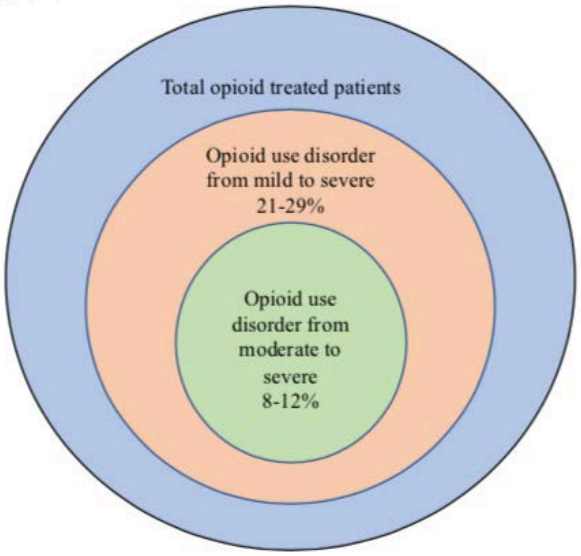
† Close reading of the Edlund text indicates that the 0.7% incidence in the article applied to the entire database, the vast majority of whom had no evidence of having used opioids. Since the other data points in the Vowles analysis were taken from populations that had all been exposed to prescription opioids, that should have been the source for the Edlund data set as well. The 7.3% incidence rate is found in the Edlund (2007) study, based upon the correct population of opioid-exposed individuals.

Figure 1. Estimates of misuse, abuse, and addiction of opioids among chronic pain patients



* Estimated from a systematic review of 38 studies published by Vowles et al. (2015)

Another way to examine the studies in the Vowles review is to focus on those that are among the highest quality studies. Studies in Vowles et al. (2015) were rated by the authors based on the quality of the evidence, as assessed by sampling and data quality, adequate description of methods, and potential influence of the raters on the identification of opioid misuse and addiction. Note that the assessment of quality was not necessarily correlated to the primary purpose of the study; that is, whether or not assessment of opioid use disorder was the primary research question underlying the analytic framework. Indeed, high quality studies that assess opioid use disorder should be given higher inferential weight regardless of whether opioid use disorder was the primary endpoint. Among these studies, the prevalence estimates of addiction vary but generally are in the range of at least 5-15%. Cowan et al. (2003) reported a rate of "addiction" of 2.8% in a sample of 104 pain clinic patients in the UK who were prescribed opioids – although the authors did not assess "addiction" based on DSM or ICD criteria, but instead on their own assessment of maladaptive consequences of use, which did not include well-validated criteria such as tolerance and physical dependence. However, it should be noted that 59 of the 104 patients dropped out of the study before study completion. The rate of "addiction" – using the authors' definition – among those who remained in the study was more than double what was reported in the abstract, at 6.5%.[43] Further, this is likely an underestimate given that well-validated symptoms of opioid use disorder were not included in the definition. The highest rates of opioid use disorder, assessed based on a questionnaire that included some DSM substance use disorder symptoms, was 15.7% in a pain clinic sample of 197 patients whose charts were reviewed.[44] The summary of the evidence presented by Vowles et al. (2015) is that among chronic pain patients, an estimated 21-29% of patients meet criteria that would be characterized as between mild to severe opioid use disorder, and an estimated 8-12% of patients meet criteria that would be consistent with moderate to severe opioid use disorders. This summary is included as Figure 1 of this report. Of note, the ranges of opioid use disorder given medical use of opioids in the Vowles et al. review are supported and cited in a range of other scientific literature and consensus statements from experts.[45]

The studies in Vowles et al. (2015) overlap, though not completely, with other reviews of the topic of opioid use disorders after medical prescription.

Fishbain et al. (2008)[46] reviewed 24 studies with various definitions of "addiction" to report an average prevalence of "addiction" of 3.3%, with a range of 0 to 45%; however, there are three central limitations to the Fishbain et al. (2008) review that together suggest that the prevalence of addiction was underestimated. First, the authors assessed "aberrant drug-related behaviors" as a marker for opioid use disorder, and studies with low prevalence of aberrant drug-related behaviors were based on designs that did not allow for comprehensive assessment of addiction. For example, Appendix 1 of Fishbain et al. (2008) includes data from 23 studies that assessed aberrant drug-related behavior as assessed by clinical opinion. Of the 5 studies that reported 0% prevalence of addiction, 2 excluded anyone with a current or former history of drug use disorders, and one defined addiction as physical dependence rather than on recommended opioid use disorder nosologies. In contrast, five studies in the review assessed aberrant drug-related behavior based on opioids other than prescribed in urine, or no opioids in urine; the range of prevalences for some indicators of aberrant drug-related behavior was 13% to 40%. Five other studies assessed illicit drugs in urine and found prevalence ranges of 1.1% prevalence of cocaine use through 57% prevalence of cannabinoids or cocaine. In

summary, low prevalence of estimated "addiction" are documented in the review when using measures of addiction that are known to underestimate prevalence (e.g., clinical opinion); measures such as urine toxicology find higher rates of addiction. Second, Fishbain et al. (2008) included an assessment of levels of evidence, from the highest levels (meta-analysis of multiple well-designed controlled studies) through the lowest (case reports and clinical examples). Of studies reporting aberrant drug-related behaviors, there were no studies that were rated as the highest levels of evidence. Authors rated each study based on a series of 23 criteria that assessed quality that could be converted into a total score from 0-100. While studies below 50 were considered "low quality", the authors used a cut-off of 65 for inclusion in the review though no validity assessment was done regarding the cut-off score, which omitted several studies that have been included in previous reviews that reported prevalence of addiction from 16-19%.[34,47,48] Indeed, these omitted studies were included in a previous review by the same authors (Fishbain et al. in 1992),[49] reporting a higher rate of prevalence of opioid use disorders following medical use, from approximately 3 to 18.9%. It is also worth noting that the lead author had undisclosed ties to opioid pharmaceutical manufacturers, which may have influenced the analysis and presentation of results as well as the decision to omit studies reporting higher rates of addition.

Hojsted & Sjogren (2007) reviewed 36 studies focused on individuals with chronic non-malignant pain and with cancer pain, and found a range in prevalence of opioid use disorders from 0-50% among non-cancer pain patients, and 0-7.7% among cancer pain patients.[50] However, the wide range of definitions that were considered as part of "misuse" in the narrative review made for a vague summary of potential rates of harm, and as such the review is of little clinical and public health relevance.

Noble et al. (2010)[51] conducted a systematic review of 10 bibliographic databases through May 2009 assessing opioid use disorder among patients prescribed opioids for chronic non-cancer pain after at least 6 months of treatment. In total, 26 studies met inclusion criteria. Investigators reported that the rate of "addiction" was 0.27%, which for several reasons is not a credible estimate for the general patient population receiving opioids. First, of the 27 treatment groups assessed in the 26 studies, 18 excluded individuals with any history of substance use disorders from participation, and the remaining 9 did not state whether patients with a history of substance use disorders were excluded or not. Further, 18 studies did not assess opioid use disorders as an outcome, and thus they are not relevant to the question of opioid use disorder risk among patients. Among the 2,613 combined patients drawn across the studies reviewed as having been assessed for addiction potential, Noble et al. inappropriately concludes that addiction is rare based on a calculated "event rate" 0.27%. Among the 7 studies that reported addiction among patients, 2 reported non-zero cases, for a total of 7 cases. A closer look at the 2 studies that were used to comprise these 7 cases reveals the flawed methodology for this event rate estimate. Portenoy et al. (2007),[52] in an industry-sponsored study, reported "problematic drug-related behavior" in 13 patients among 227 who were treated with controlled-release Oxycodone for 1-3 years, for an incidence of 5.7%; an expert review panel of those 13 patients concluded that 6 had probable opioid use disorder. Problematic drug-related behaviors included symptoms of drug use disorder, seeking prescriptions from other doctors, withdrawal symptoms upon discontinuation of medication (although no other criteria for opioid use disorder was used), and other patients with suspected symptoms of opioid use disorder but without definitive evidence for a diagnosis. These reports are likely an underestimate, given that urine toxicology was not performed, and that patients receiving opioids under-report opioid use disorder symptoms. Further, the sponsorship of the study by industry suggests that there was a financial interest in reporting a low number of opioid use disorders in the patient population, suggestive of bias due to financial conflicts of interest. The other study cited by Noble et al. (2010) as evidence for low risk of opioid use disorders was Anderson et al. (1999),[53] a study of 30 individuals prescribed intraspinal morphine and followed for 24 months on average. One patient among the 30 was described as having "drug-seeking behavior", and was thus included in the Noble et al. (2010) review as a case of addiction. However, it should be noted that within this 30 person trial, 3 persons died and 5 more had only partial follow-up data; the remainder were not systematically assessed for opioid use disorder. Thus the actual event rate is unknown. To infer an event rate of 0.27% based on 7 cases reported in 257 patients, many of whom were not systematically assessed for opioid use disorder or assessed with urine toxicology, based predominantly on one industry-funded study, is inappropriate and not scientifically rigorous.

Minozzi et al. (2012) reviewed 17 studies involving 88,235 patients that subsumed systematic reviews, one randomized trial, eight cross-sectional studies and four case series.[54] The majority of studies included patients with non-cancer chronic pain who had been treated with opioids for long periods of time. Recorded incidence of opioid use disorders across these studies ranged from 0 to 24%, and prevalence ranged from 0 to 31%. However, again, many of the studies assessing non-medical opioid use, and opioid use disorders, among medical users likely had underreporting and undercounting of opioid use disorder symptoms, as they were based primarily on chart review rather than structured diagnostic interviews and/or urine toxicology. Further, the length of opioid duration varied substantially, including periods of only 3 days duration or 10 days or more within a month after which opioid use disorder would not be expected to occur at substantial rates (because of intermittent rather than continuous use). The strong evidence base is that opioid use disorder occurs with increased frequency as dose and duration increase, thus assessing opioid use disorder when combining short episodes of use with longer episodes obscures this important finding. Further, Minozzi et al. included data that overlapped with Noble (2010) and Fishbain 2008), which I found unreliable for reasons that are previously described.

Martell et al (2007)[55] focused on patient populations with chronic back pain. The authors reviewed 4 studies that reported prevalence rates of aberrant drug using behavior which ranged from between 3 and 43%, which is in line with the review by Vowles et al., which focused on a broader patient population but had prevalence estimates of addiction in the same range. Further, Martell et al. (2007) also included analysis of 5 studies that reported substance use disorders, which were reported by approximately 36% to 56% of patients included in the studies.

Finally, Higgins, Smith, and Matthews (2018)[56] purportedly aims to review the incidence of opioid use disorder among patients in pain who were prescribed opioid analgesics. My assessment of this review is that it does not address the research question that it aimed to address, and lacks methodological rigor to the extent that it is not a reliable assessment of opioid use disorder risk. I make these assessments for the following reasons. Higgins et al. include studies that do not meet their stated inclusion criteria. Among the stated criteria included populations in which interventions with opioid analgesics were performed, and incidence of opioid use disorder was assessed. Yet several studies do not meet these criteria. For example, Dersh et al.[57] assessed previous opioid use disorder at the time of entry into the study population, and did not introduce any opioid intervention; the study does not assess opioid use disorder incidence, nor do they claim to do so. Opioid use disorder prevalence at entry was incorrectly reported as the study incidence in Higgins et al.[56] Additionally, Adams et al. (2006)[58] excluded patients with current substance abuse 'problem' (based on physician judgement), but not past history of opioid use disorder, which would be the correct exclusion to estimate incidence. Similarly, Cowan et al. (2002),[59] a pilot study of only 22 patients, does not exclude patients with prior opioid use disorder. Thus, the systematic review does not assess the stated goal of estimating incidence. Most problematically, the article reports on an overall association between any opioid use and opioid use disorder, but this association is uninformative and essentially pointless. It is well-documented that risks of opioid-related adverse outcomes are heterogeneous by dose and duration of use. Without assessment of these two factors, the review paper is far from what is standard in the literature at this point in opioid epidemiology. Higgins et al. use an assessment of "strong" versus "weak" opioids, based on product, without considering dose and duration of MME based on any standard conversion. This is not a valid or well-accepted assessment of opioid strength. Further, Several studies included in Higgins' review (e.g. Edlund et al. 2014)[60] have critical information on both dose and duration that could be used to inform a more accurate assessment of the risk of opioid use disorder, but such information was omitted from the Higgins manuscript. For example, authors cite an opioid use disorder incidence rate of 0.2%, purportedly derived from Edlund, but this is largely (almost 95%) based on patients who had acute (short duration) opioids, thus not an appropriate assessment of the overall effect of opioid therapy on opioid use disorder at all doses and durations. The Edlund article itself points out that it is inappropriate to present overall rates, where the data show a 50-fold difference between the rate for low-dose, acute opioid users compared to high dose chronic opioid users. This same issue underlies Cepeda et al. (2013),[61] which was also included in the Higgins review; the study includes data for almost 40,000 patients from insurance claims databases and reports an overall association between opioid prescriptions and claims-recorded opioid use disorder, without disaggregating the

dose or duration. Such information is uninformative for assessment of opioid use disorder risk with prescription opioid use, given the known heterogeneity. Further, the outcome of opioid use disorder is inadequately assessed in many of the studies included in the review. For example, several studies used the presence of ICD-9 or ICD-10 codes in patient charts as an assessment of study outcome. These chart diagnoses are known to underestimate opioid use disorder. Additionally, there are several areas where scientific rigor is undermined throughout the Higgins et al. review in terms of framing limitations and comparing results with more rigorous work. Studies routinely disclose that their incidence estimates are likely underestimates due to generally accepted limitations of such data (e.g. those of Edlund et al.); Higgins et al. does not list the underestimation of outcomes as a limitation, which is concerning for the scientific accuracy of the work. Higgins inaccurately discusses consistency with the Vowles 2015[62] study as evidence of the strength of Higgins' analysis. However, Higgins incorrectly states that Vowles reached a conclusion similar to their own, as to the rates of addiction (4.3 v. 4.7%), when in fact Vowles reported a much higher rate of addiction (8-12%), or approximately 21-29% when the spectrum of mild through severe OUD is included. In summary, this systematic review is largely uninformative. There are errors in article inclusion, coupled with the lack of informativeness of the exposure category, and the lack of validity of the outcome assessments, which in total render the systematic review of little scientific value.

In summary, the range of reviews available on the risks of "misuse" and "addiction" of prescription opioids from medical use vary because of differences in inclusion criteria and definitions. However, the results of multiple studies with a wide range of designs indicate that risks are high when opioids are prescribed in large doses for long periods of time, with available and reliable estimates indicating that opioid misuse rates range from 21-29% (corresponding to opioid use disorder ranging from mild to severe), and that opioid addiction risk among this group ranges from approximately 8-12% (corresponding to opioid use disorder ranging from moderate to severe), with even higher rates when assessing individuals who are on high doses of opioids for long periods of time.

More recent studies that were not included in aforementioned reviews also provide evidence that risks of opioid use disorders are substantial after medical use. Using a large pharmacy and medical claims database from 2000 to 2005, Edlund et al. (2014) documented that the risk of chart-documented opioid use disorders increased with both dose and duration of opioid use in a large health services database of adults.[63] The majority of the sample were either non-opioid users (65% of the sample), or those who had been prescribed opioids for acute pain (94.1% of those prescribed opioids). Among those who had high dose opioids for a greater number of days, the risk of opioid use disorders was in line with what previous reviews and meta-analyses suggest is the range of prevalence estimates for opioid use disorders among medical users, at 6.1% incidence of new opioid use disorder. The level of risk of incident opioid use disorder varied according to the dose and length of opioid use, and there was a dose-response relationship between dose and length of opioid use and incident opioid use disorder diagnosis including high daily dose (≥100 MME), and long-term opioid use (>3 months), with highest risk of opioid use disorders observed among persons prescribed high doses (≥120 MME) for long-term use (91+ days). Indeed, among these patients, the risk of incident opioid use disorders was 122.5 times higher than those with no opioid use, after adjustment for age, sex, indicators of pain and mental disorders, and the estimated incidence was around 6% for these individuals. But even at very low levels of use, the risk of opioid use disorder diagnoses was significant. Among those with acute (1-90 days of use) opioid use at a low dose (1-36 MME), risk of incident opioid use disorders was 3.03 times higher than those with no opioid use. There is also undercounting of opioid use disorders using clinical records. Edlund et al. (2014) relied on incident diagnoses with a relatively short window after opioids use, which would not capture those with recurrent opioid use disorder symptoms or those who did not develop symptoms shortly after use. Thus, as the authors acknowledged, total burden is likely underestimated, and may be considered a lower bound of all potential harm. Of note, as summarized in the definitions section of this report, the DSM-V changed the diagnosis of opioid use disorder diagnoses to exclude those who have tolerance and withdrawal but no additional symptoms when under 'appropriate' medical supervision. As outlined in Section B of the report, this decision was not based on empirical evidence, and thus to the extent that DSM-5 diagnoses were used in studies that assess opioid use disorder, prevalence is likely underestimated even further.

Finally, Boscarino et al. (2015)[64] utilized data on patients randomly selected from outpatient clinical records who were receiving care for non-cancer conditions such as pain, arthritis, and orthopedic conditions and had been prescribed five or more prescription opioid medications in a 12 month period. Patients consented to structured interviews for opioid use disorder based on DSM-IV and DSM-5 criteria (N=705). Among these patients, 28.1% had 2-3 symptoms of opioid use disorder (designated in DSM-5 as "mild" disorder), 9.7% had 4-5 symptoms ("moderate" disorder), and 3.5% had 6+ symptoms ("severe" disorder), for a total prevalence of any opioid use disorder from mild to severe of 41.3%. These rates are remarkably consistent with Vowles et al. (2015), in that the prevalence of "addiction" was estimated between 8-12%, which is consistent with the total of moderate and severe opioid use disorder reported by Boscarino et al., in that moderate and severe opioid use disorder together would be an estimated 13.2%. Further, Vowles et al. (2015) estimated that the prevalence of opioid "misuse" was between 21-29%, which is consistent with the 28.1% prevalence from Boscarino et al. for "mild" opioid use disorder. Such evidence of consistency provides additional support for the reliability of the results.

Risks of opioid use disorder after prescription opioid use are not solely determined by dose and length of opioid use. Individual risk-factors for opioid use disorders include younger age (e.g., 18-30), lifetime history of psychoactive illicit drug use, and lifetime psychiatric or substance use disorder. However, risks for opioid use disorder based on dose and length of opioid prescription persist even when controlling for these risk factors, and the magnitude of the association for dose and duration of opioid use are greater than individual-level risk factors for opioid use disorders, even when taking them all into consideration together. Nevertheless, the burden of opioid use disorders following medical prescription of opioids, especially at high doses and for long duration, is especially greater among those who already have vulnerabilities to addiction. Indeed, results of studies that exclude those with a history of drug use disorders from inclusion in the study sample are not generalizable to the total patient population of individuals receiving opioid medication therapies due to the higher baseline risk for addiction.

Generally, the existing evidence likely underestimates the total burden of opioid use disorders. Even in the setting of high-quality evidence and structured diagnostic interviews with adjunctive evidence through urine toxicology, existing studies routinely underestimate opioid use disorder. Less than half of substance use disorders identified in community samples are even diagnosed and/or treated in medical settings, and thus a substantial portion, upwards of half, of total diagnoses are likely missed throughout studies that recruit and treat patients in medical settings. Further, studies using urine toxicology screens, validated instruments for opioid use disorder, and other high-quality objective indicators demonstrate a higher proportion of opioid use disorder than studies relying on administrative records that are not collected for research purposes.[65,66] Studies that use diagnostic questionnaires provide assessment of opioid use disorder that are more valid than case files, though may still underestimate rates of opioid use disorder, especially in medical settings where patients may not want to disclose problems related to medication usage. Diagnostic interviews coupled with urine toxicology identify more cases than either alone. For example, Katz et al. documented that 21% of patients with no behavioral symptoms of substance use disorder had positive urine screens for illicit drugs or non-prescribed controlled medication, and 14% of those without positive urine toxicology had evidence of substance use disorders in a sample of 122 patients maintained on long-term opioids for non-cancer pain.[67] Additional studies have also provided evidence that urine toxicology identifies individuals with drug use disorders among those who deny such use in interviews among medical opioid users,[65] suggesting that the combination of urine toxicology plus structured, validated self-report measures, together provide rigorous data to assess drug use disorders among medical users of opioids.

Further, opioid use disorder is likely underestimated when using DSM-5, because the criteria of "tolerance" (needing more of the drug to get the same effect) and "withdrawal" (manifesting symptoms when the drug is not taken) were generally considered diagnostic of OUD, but those criteria could *not* be considered diagnostic of OUD when they were observed among individuals taking opioids solely under 'appropriate' (based on the DSM-5 definition) medical supervision. This distinction, however, is fraught with error that renders this decision from DSM-5 to be an erroneous one that results in misclassification. There is no scientific evidence that individuals with these two criteria have a different pathology or course of disorder

compared to individuals with any other two criteria, or that individuals who have these two criteria and who use opioids non-medically have any differences in course or consequences than individuals who have these two criteria who use opioids under medical supervision. The very notion that the medical supervision of opioid use would have any impact on the course of opioid use disorder among those who the same symptoms of opioid use disorder defies logic. Further, 'appropriate' medical supervision is not defined, and presumes that physicians have scientifically accurate and independent information about the risks and benefits of opioid prescribing which previous research has demonstrated is far from ubiquitous. Indeed, as well documented in other sections of this report, opioid use disorder is common among individuals who obtain opioid prescriptions from a physician, with approximately 21-29% of patients exhibiting mild to severe opioid use disorder. Mikosz et al. (2020) indicate that physicians prescribing opioids at quantities and durations beyond recommended guidelines for many indications remains a significant problem in the US, thus the notion that currently prescribing practices are 'appropriate' is not consistent with the available evidence.[68] Further, there is evidence that industry influence played a role in creating this hierarchical exclusion, as the committee included a consultant for pharmaceutical companies that produce opioids,[69] thus representing a conflict of interest,[70] and, as a result the decision to restrict the diagnoses from those patients with these two criteria, erroneously supported an industry-favored narrative. I have contributed extensively to the literature on psychometric properties of substance use disorder criteria,[71–76] in evaluating the scientific evidence for the structure and dimensionality of substance use disorder criteria in both general population and clinical samples. I did this work primarily during the years in which potential changes from DSM-IV in preparation for DSM-V were being evaluated (I had no role on the committee).[77] My work, as well as others (reviewed here[77]), demonstrated that substance use disorder criteria (including tolerance and withdrawal) are unidimensional, indicating that they are statistically correlated and underlie graduations in a similar underlying spectrum of substance use disorder severity. There is no statistical evidence to indicate that those who experience tolerance and withdrawal alone have a fundamentally different disorder or set of outcomes compared with individuals who experience any two other symptoms, especially based on where the opioids were obtained. Indeed, numerous epidemiological studies indicate that they are reliable indicators of substance use disorder and statistically corrected with other indicators of substance use disorder. Thus, the scientific rationale behind excluding individuals who experience tolerance and withdrawal from medical prescriptions of opioids is unpersuasive; the fact that tolerance and withdrawal are expected consequences of continued use of opioids has no bearing on their validity as symptoms of dysfunction. It is my opinion that withholding a diagnosis of substance use disorder based on tolerance and withdrawal alone is not consistent with the epidemiological literature concerning substance use disorders.

In summary, there is a wide range of reported prevalence and incidence estimates of opioid use disorders. The reasons for this range include the characteristics of the samples (e.g., pain conditions, amount and types of opioids used, individual-level patient characteristics that predispose individuals to developing opioid use disorder) as well as the measurement of opioid use disorder, sample size and study design. However, the high-quality evidence across reviews indicates that the risk of incident opioid use disorders, as well as recurrence of opioid use disorders, increases in a dose-response fashion with the dose of opioids and the length of opioid use, even after controlling for individual-level predisposing factors, and that 21-29% of chronic opioid users have mild, moderate or severe OUD. Importantly, the evidence is clear that risks of opioid use disorder following medical use of prescription opioids follow a "dose-response" pattern, supporting my opinion that there is a causal relationship between prescription opioid exposure and opioid use disorder.

C. Opioids were diverted and used by individuals with opioid use disorder and for non-medical use

Diversion of opioids occurs at many points along the supply and distribution pipeline, and generally is considered to occur when opioids are transferred from an intended recipient to an unintended recipient. This broad definition underlies multiple pathways in which opioid diversion occurs; the end result in all mechanisms of diversion is non-medical use of opioids. Two common pathways to diversion are those that are due to: (a) pervasive overprescribing to consumers, and (b) pervasive oversupply from high volume facilities and pharmacies distributing extraordinary quantities of opioids.

Pervasive overprescribing resulted in unused prescribed opioid medications diverted for monetary value, barter, or for no cost among family and individuals in a shared social network. Receipt of prescription opioids from a friend or family member is a common mechanism, which is the result of a high level and volume of prescribing of opioids that are unnecessary to control pain in many patients. Available estimates indicate that 90% of patients prescribed opioids after surgery have unused medication,[78–80] most of which is not disposed of or stored safely.[81] Thus, the high volume of opioid prescriptions, both in routine prescribing and through high volume prescribers and facilitates that were unchecked in distributing massive quantities of opioid pills, became the foundation for the overall expansion in the opioid supply and opioid related harm. This is evident in that that close to 98 million Americans receive prescription pain relievers every year, a much larger number than the estimated 12.5 million who use opioids non-medically,[8] suggesting that the expansion of opioid sales and distribution served as a catalyst for the overall ability of these medications to be diverted through social networks. Data from the National Survey on Drug Use and Health (NSDUH) from 2013-2014 indicates that among non-medical opioid users interviewed about where they obtain their opioids, 50.5% report from a friend or relative.[82] Other data sources on drug diversion converge in supporting the fact that the common routes for opioid prescriptions on the illicit marketplace are drug dealers as well as family and friends. Inciardi et al. (2009)[83] reviewed a number of studies that estimated illicit sources of prescription opioids. Data from the NSDUH, a national sample primarily from households in the general population, show that 57% of non-medical opioid users in 2007 obtained opioids from a friend or relative for free, with another 9% reporting that friend or relative for purchase was also a source of opioids. Of those reporting their source as a friend or family member, approximately 80% of these friends or family members are reported to have received opioids from a single prescriber, indicating that at least a fifth of individuals who received opioid prescriptions did so from a friend or family member who was receiving opioids from multiple prescribers. In contrast to users in treatment, a relatively small proportion of individuals in the NSDUH obtained opioids from a drug dealer (individual or group who explicitly sell illicit opioids for profit). Data sources focused on adolescents and young adults support these findings; a large survey of college students found that peers and family were the most common sources of prescription opioids.[84,85] Further, availability of prescriptions from a family member is associated with harms due to opioids; for example, a large case-control study using data on prescribed opioids from a commercial insurance database linked to hospital records indicated that opioid dispensing to family members is associated with 3 times the risk of prospective individual hospitalized overdose, and that the relationship increased with the dose prescribed to a family member.[86]

Pervasive oversupply led to diversion of opioids through medical providers for the purpose of non-medical use, including individuals obtaining multiple prescriptions across providers, as well as through high-volume prescribers that were not properly regulated. Medical sources of prescription opioids that are diverted for non-medical use are also common. Shei et al (2015)[87] analyzed data among 9,291 commercially insured patients aged 12-64 who had a recorded diagnosis of opioid abuse or dependence (per medical record, thus unclear whether based on DSM criteria or clinical judgement), and 395,901 comparison individuals with no diagnosis. It is important to note that a record of opioid abuse/dependence is likely a drastic undercount of the actual proportion of individuals who would meet criteria for OUD, given that there was no systematic validated interview of individuals in the study and no toxicology performed. Nevertheless, allowing for this limitation, Shei et al. (2015) document a high proportion of medical sources of opioids for diversion. Among those with an opioid abuse/dependence diagnosis in the medical record, 79.9% had at least one claim for a prescription opioid prior to diagnosis. The high rate of medical sources of opioids among those with opioid use disorder also support my opinion that patients using opioids under medical supervision are at risk for developing opioid use disorder. Furthermore, among those with no prior prescription for an opioid, an additional 10% had a family member with at least one prior prescription for an opioid, suggesting that diversion from family or friends could also contribute to OUD diagnoses within this sample. Indeed, overall, 50.8% had a family member with an opioid prescription claim, compared with 42.2% of patients with no diagnosis. Additional evidence for diversion having occurred is that 20.1% of those with an opioid abuse/dependence diagnosis had no record of a prescription opioid. Overall prescribing rates in the sample were high; among this group of individuals who were receiving medical treatment of some kind,

even among those with no OUD diagnosis, 56.8% of patients had a prescription for opioids. However, it is worth noting that while these individuals did not have an OUD diagnosis on their medical record, under-ascertainment of OUD in medical settings is common. Also of note, the study was not able to distinguish whether those with OUD who had no record of prescription opioids used prescription opioids, heroin, or other forms of opioids. Importantly, however, the study was industry funded and the authors of Shei et al. (2015) are comprised of pharmaceutical manufacturer employees and consultants; thus the finding that medical sources of opioids are found in the vast majority of individuals with OUD, even more than individuals without a notation of OUD in their medical record, could be considered likely conservative given that they indicate strong overlap between the supply-side sources of prescription opioids and the development of OUD.

Individuals who misuse opioids and/or develop OUD are likely to obtain them from multiple available sources, including physicians and other providers, sometimes multiple physicians. Data from the NSDUH from 2013-2014 indicate that while family/relative is the most common source of non-medical prescription opioids, 25.1% obtain opioids from at least one physician.[82] Among the various samples of users reported by Cicero and colleagues (2011),[88] medical sources of prescription opioids were commonly reported. For example, among 1,983 individuals in treatment for opioid dependence, 25% reported that their primary method of obtaining access was through doctors, and more than 50% reported that doctors were among the various methods of obtaining opioids. Among the sample of 782 individuals in substance abuse treatment collected in South Florida, 13.8% reported obtaining opioids from a medical practice (however, it should be noted that these results were assessed prior to the restrictions on high-volume prescribing in Florida, thus may not be generalizable to more recent years).[88] In a study of 346 individuals with prescription opioids as a primary drug of abuse and in methadone maintenance, 20% reported doctors as a primary source, and 9% reported emergency rooms.[83] Data from the NSDUH study indicated that among those who reported non-medical prescription opioid use, 18% reported that they obtained opioids for non-medical use from a doctor, although information is not available

Further, another mechanism through which individuals obtain opioids for non-medical use is the practice of visiting multiple providers, so-called 'doctor shopping'. The practice of obtaining multiple prescriptions across providers is frequently reported among individuals with prescription opioid use disorder.[89] The prevalence of multiple-provider visits for the purpose of obtaining opioids for non-medical use is complicated to estimate given that there is no empirical flag in the data for the purpose or medical need for prescription opioids. Multiple prescribing can indicate individuals who are recklessly seeking opioids for non-medical personal use and sale, or could be indicative of poorly managed care.[90] McDonald and Carlson (2013) estimated prevalence using a probabilistic algorithm that took into account the number of unique providers within a given time period that prescribed opioids per person using data on commercially insured patients in the United States, including more than 146.1 million prescriptions for opioids written in 2008. On average, among patients who received opioid prescriptions, 14% received additional prescriptions from at least one more provider, 3% of these patients obtained additional prescriptions from between 5-9 providers, 0.35% from 10-19 providers, and 0.04% from 20 or more.[91] In a follow-up analysis, McDonald and Carlson (2014) also estimated the extent to which there is geographic variation in the estimated predicted prevalence of multiple provider use. Using a predicted estimate of probable 'doctor shoppers' based on outlier data on individuals who used a suspiciously high number of providers to obtain multiple prescriptions, investigators determined that the prevalence varied across counties from 0.6 per 1,000 and 2.5 per 1,000. The overall mean prevalence across states indicated that doctor shopping is relatively rare in comparison to the high quantity of opioids that have flowed into the medical market, with a mean of 0.7 per 1,000. The prevalence of probable 'doctor shopping' increased with the prevalence of the general prescribing practices of various geographic locations, indicating that as the supply of opioids increased, so too did diversion for non-medical use, including through individuals 'doctor shopping'.[92] The population estimates of multiple-prescribing episodes generally range from <1% to between 7-9%, depending on the criteria used to define 'doctor shopping'. The variation in the population estimates of multiple prescribing indicate substantial variability, and studies that were funded by the pharmaceutical industry generally publish lower estimates of 'doctor shopping' than independent scholars,[93] indicative of the industry's financial interest in suggesting low rates of diversion.

Among Tennessee Medicaid recipients from 2003 to 2010,[94] 7.6% of patients prescribed opioids received medication from 4 or more pharmacies within a one-year window, and these patients had almost 7 times the odds of a subsequent overdose death. Data from Medicaid recipients in 2016 estimated the prevalence of 'doctor shopping' to be 3.9% among 66,328 patients, defining shopping as the receipt of opioid prescriptions with greater than 1-day overlap filled at 3 or more pharmacies within a 6-month period. While the expansion of prescription drug monitoring programs in most states is intended to reduce the practice of uncoordinated care that can result in multiple provider visits and the potential for individuals intentionally obtaining opioids for the purpose of misuse, there is wide variation in the strength and implementation of prescription drug monitoring program (PDMP) policies and questionable effectiveness in many jurisdictions.[95–97] Data on PDMP policies have been specifically evaluated for West Virginia, including policy mandates on health care licensing based on adoption of PDMP use, as well as PDMP usage requirements for pain-relieving controlled substances for chronic- non-malignant pain. Strickler et al. (2019)[98] examined prescribing data from the Prescription Behavior Surveillance System from 2010 to 2017. Using regression discontinuity approaches, Strickler et al. (2019) document that the PDMP mandates had little impact on PDMP usage in West Virginia, compared to increased usage in other states like Kentucky; and had little impact on prescribing as well. While this specific study found limited impact of West Virginia's PDMP program on prescribing from 2010 to 2017, West Virginia has implemented a range of additional efforts to reduce opioid prescribing that are hypothesized to in part underlie the decrease from 2011 to 2018 of hydromorphone (from 100 million to <38 million) and oxycodone (from 44 million to <25 million),[99] but the high level of prescribing (indeed, substantially higher than the national average) continues to require additional intervention. Furthermore, evaluation of overdose decedents in West Virginia indicate that there is substantial evidence for harm associated with doctor shopping and diversion; among 295 decedents in West Virginia in 2006, there was evidence that diversion contributed to non-medical use in 63.1% of cases, and doctor shopping was present in 21.4% of cases.[100]

In summary, there is variation in the literature in the definition of 'doctor shopping', but despite variation, there is consistent evidence that diversion of opioids through individuals obtaining multiple prescriptions for the purpose of non-medical use or sale occurs with regularity. Further, that 'doctor shopping' increases in prevalence as the overall supply and dispensing of opioids increases across jurisdictions in the United States. While prescribing of opioids has declined in West Virginia since 2011, overall prescribing patterns remains extraordinarily high, especially in Cabell County.

In addition to patients who intentionally visit multiple prescribers to obtain opioids in order to divert them, there is also evidence of diversion of prescription opioids through high-volume providers who inappropriately prescribe opioids for profit (often referred to as "Pill Mills"). Available evidence indicates that Pill Mills created considerable damage to population health in many areas of the United States throughout the 1990s and 2000s, although in a context of an extraordinary and voluminous increase in opioid prescribing across almost all medical specialties. Indeed, studies of high-volume prescribing indicates that there are certainly prescribers with an extraordinary volume of prescriptions, both in West Virginia and elsewhere; those in West Virginia can be identified through IQVIA and other prescribing data that include prescriber and prescriber identifiers. Guy & Zhang (2018) reported that, of the 209.5 million opioid prescriptions dispensed in the United States between July 2016 and July 2017, the average yearly prescription volume was 215.8 prescriptions per provider, but that some specialties prescribed on average up to 1,314.9 per provider.[101] Similarly to PDMP policies, there has been a concentration of legislative work to regulate and close high-volume prescribers,[102] with variable implementation and effectiveness across states.[96,103–106] These laws typically include requirements for annual licensing, place limits on the number of patients to providers, and include prohibitions on dispensing of opioids at the same location as the provider. Numerous studies have examined high-volume prescribing laws in diverse states such as Florida,[106,107] Texas,[108] Ohio and Tennessee,[109] and such laws are generally associated with reductions in prescribing, overdose death and other harms, although they are typically packaged with other laws, such as PDMPs, and thus these studies typically capture their combined effects. Despite these legislative and law enforcement efforts, high-volume prescribing remains an important source of opioid-related harm. Available data indicate that prescribing of opioids increased across many specialties in medicine, and while some specialties of medicine have a more

concentrated prescription practice for opioids (e.g., pain, anesthesia, and physical therapy), general practitioners in family and internal medicine dispenses the greater number of opioids, widespread across geographic areas of the United States.[110]

Summary. A substantial portion of the opioid crisis has arisen due to the diversion of prescription opioids from medical to non-medical uses. These include the vast availability of opioids in American homes due to oversupply and over-prescription, from which opioids were traded, given, or sold within social networks. It also includes individuals who sought multiple prescriptions in order to use non-medically and/or sell, as well as high-volume prescribers who did not prescribe based on legitimate medical need. All three of these streams of over-supply have contributed to the increase in opioid use disorder, overdose, and related harms in the United States.

D. The incidence and prevalence of both medical and non-medical opioid use increased in concert with the increased supply of opioids

The evidence is clear that the opioid supply increased dramatically in the United States beginning in the mid 1990s; that medical use of opioids is causally associated with the development of opioid use disorder; and that diversion of opioids occurred. The increased supply of opioids contributed substantially to an increase in the incidence and prevalence of non-medical opioid use and non-medical opioid use disorder in the general population. Evidence regarding non-medical prescription opioid use in the general population is not generally available before the early 2000s for adults. Among adolescents, data can be drawn from the Monitoring the Future study, a large, annually conducted survey of high-school attending adolescents. Among students in the 12th grade, for example, use of "narcotics other than heroin" increased annually beginning in 1992, from 3.3% to a peak of 7.0% in 2000. In 2002, the question wording and example changed, thus trends before and after 2002 cannot be directly compared. McCabe et al. reported these trends in prevalence in both medical and nonmedical use in a 2017 publication in *Pediatrics*, noting that adolescent non-medical use of opioids is frequently preceded by medical use.[111] The prevalence of narcotics other than heroin has been generally declining among adolescents since the early 2000s.[112]

While prescription opioid use has been declining among adolescents, among adults, trends indicate that prescription opioid use is stable, with generally low magnitude declines since 2012 but still a high burden of harm for heavy use and addiction. Martins et al. (2010) documented birth-cohort trends in non-medical prescription opioid use and opioid use disorder by comparing two surveys: one conducted in 1991-1992, and another, using the same sampling frame and measurement questions, in 2001-2002. The study found that among adults, past-year non-medical prescription opioid use increased by 44% (from 0.9 to 1.3%) across the decade, and that past year prescription opioid use disorder increased by 55% (from 0.2 to 0.3%). Among those who reported non-medical prescription opioid use in their lifetime, the prevalence of past-year opioid use disorder increased 89.6% (from 4.8 to 9.1%).[113]

Other data can be drawn from to infer trends in non-medical prescription opioid use during the 1990s and 2000s. Crane (2015), for example, documented that emergency department (ED) visits for non-medical prescription opioids use from 2005 to 2009 increased over 200% among those aged 18-34 years old, a greater increase than any other age group.[114] Analyses of the Drug Abuse Warning Network (DAWN) data have found increases in ED mentions of opioid analgesic misuse through 2011; for example, the number of ED mentions of oxycodone increased from 41,701 in 2004 to 151,218 in 2011. Total for all pharmaceutical opioids, ED mentions increased from 152,827 in 2004 to 404, 829 in 2011.[115] Finally, data from the Treatment Episode Data Set indicate that from 2005 to 2015, the proportion of individuals entering treatment with prescription opioid use as the principal drug for services increased from 18% to approximately 38%.[116]

More recent data generally show that the prevalence of non-medical prescription opioid use is stabilizing or beginning to decline, depending on the population and outcome, but that burden remains substantial. For example, data from the NSDUH indicate that among those 18 through 64, the prevalence of non-medical prescription opioid use decreased from 5.4% in 2003 to 4.9% in 2013. However, the same study documented that harms related to opioid use remained on the rise, with increased prescription opioid use disorders,

frequency of use, and mortality (mortality will be reviewed in detail in Section E).[117] Indeed, from 2003 through 2013, the prevalence of opioid use disorders, among the surveyed population as a whole, increased from 0.6% to 0.9%; high frequency use increased from 0.3% to 0.4%. Among users, the prevalence of opioid use disorder increased from 11.9% to 17.8%, and high frequency use increased from 5.0% to 8.2%, and mean days of use increased from 40.0 to 54.2 days. Comorbidity with other drug use disorders ranges from risk ratios of approximately 1.50 to 2.0.

Important to consider in interpreting the evidence are limitations of survey data sources, which consistently underestimate the populations at highest risk of opioid-related harm. Existing survey data sources capture rates of non-medical opioid use and opioid use disorder among those living in households and group quarters as the explicit sampling frame. Such surveys do not include high risk populations, such as those incarcerated and homeless. Existing research demonstrates that survey responders are generally healthier than the general population,[118] and thus fewer individuals using opioids non-medically and those with opioid use disorder will be captured in these data systems compared to the actual burden in the population. Indeed, heavy opioid use is associated with criminal justice involvement and homelessness,[119–121] thus I would expect that those with the highest burden of use would be least likely to be captured in household-based surveys. However, higher opioid use among these at-risk groups (housing insecure, incarcerated individuals) also would not occur without access to opioids through an increased supply that began with the widespread pharmaceutical distribution, thus the exclusion of these groups from the sampling from of survey sources does not change my conclusions. Nevertheless, while estimates of prevalence are likely underestimated, the trends over time should not be affected as long as underestimation is consistent across time.

Further, survey data sources regularly query explicitly non-medical prescription opioid use, and do not collect information on the portion of respondents who also used opioids medically, either prior to or concurrently with non-medical prescription opioid use. However, data indicate that a substantial portion of non-medical users obtain opioids at some point from physicians for medical uses (see Section C for discussion of and reference to patterns of physician contact among non-medical users).

In summary, the expansion of non-medical prescription opioid use would not have occurred without the widespread availability of prescription opioids, often prescribed in extraordinarily high quantities for a wide range of indications for which they were unnecessary based on assessment of the epidemiological evidence,[68,122] leaving a surplus of opioids that could be diverted for non-medical uses. There is clear and unambiguous evidence to conclude that non-medical prescription opioid use, prescription opioid disorder, and ED visits for prescription opioid use increased in the US population from the 1900s through the late 2000s. Available evidence indicates declines in overall non-medical prescription opioid use in recent years among both adolescents and adults, but there remain steady increases in heavy use and opioid use disorders, indicating that the burden of harm remains high.

E. The increase in the prescription opioid supply, coupled with opioid use disorders and increases in non-medical use and non-medical opioid use disorder, resulted in an exponential increase in prescription opioid overdose as well as many other non-fatal consequences.

Data on the increase in prescription drug overdose deaths in the United States are primarily drawn from the National Vital Statistics Surveillance System. In 2000, the overdose death rate attributed to prescription opioids was 1.4 per 100,000 (representing 4,030 designated deaths). By 2003 the rate had more than doubled to 2.9 per 100,000 (representing 8,517 designated deaths), and the rate continued to increase yearly until approximately 2010 (at a rate of 5.4 per 100,000, representing 16,651 deaths).[123] From 2010 to 2014, the rate remained relatively stable, albeit a quadrupling of the rate that was observed in 1999, after which increases in the overdose death rate renewed. Heroin and synthetic opioids began an exponential increase after 2010, and overdose rates due to heroin and synthetic opioids continued to climb. However, it is important to note that prescription opioid deaths remain an important contributor to overall overdose deaths, even as heroin and synthetic opioid deaths rise exponentially. I examined the rates of opioid overdose from 2016 to 2017 based on two sets of causes of death: (1) all natural, semisynthetic, and methadone opioids; and (2) natural and

semisynthetic opioids alone. The rate of natural, semisynthetic category, when including methadone overdose, has remained virtually unchanged, at 5.2 per 100,000 in each year, representing 17,087 deaths in 2016 and 17,029 deaths in 2017.[124] Considering those deaths designated as natural and semisynthetic opioids alone (i.e. excluding methadone deaths), death rates are also consistent from 2016 to 2017, indicating a high burden of harm.[125] In 2016, the death rate for natural and semisynthetic opioids was 4.4 per 100,000 (representing 14,487 deaths), and remained at 4.4 per 100,000 in 2017 (representing 14,495 deaths).

There have been rapid increases in opioid overdose death due to heroin and synthetic opioids, with heroin deaths beginning to increase in approximately 2011-2013, and synthetic opioids beginning in approximately 2013-2015.[126] While these increases are concerning, it is important to note that they remain overshadowed by the total burden of prescription opioids overdose deaths. Examining the total number of overdose deaths due to natural and semisynthetic opioids, which would exclude heroin and fentanyl deaths, there have been a total of 175,004 deaths since 1999 through 2018. This number of deaths is greater than the recorded deaths from heroin over the same time period (N=115,568) or the recorded number of deaths due to non-methadone synthetic opioids (N=124,486). When considering semisynthetic opioids and methadone, a recent CDC publication indicated that the number of prescription opioid deaths was 17,029 in 2017 and 14,975 in 2018,[3] suggesting that the burden of prescription opioid overdose in the United States remains high, underscoring the public health burden of prescription opioid overdose. Provisional data released by the CDC in July 2020 indicate that over 70,000 individuals in the US died of overdose in 2019, an increase from the death rate in 2018, suggesting that the devastation to human life caused by the overdose crisis continues.[2]

The empirical literature demonstrates a strong and statistically significant association between the opioid supply and the increase in prescription opioid deaths. In the United States, Paulozzi & Ryan (2006),[127] documented the distribution of prescription opioids, based on data from the ARCOS. Scholars estimated the total rate of prescription opioid dispensing per 100,000 in each state in 2002, and correlated it across states with the drug poisoning death rate per 100,000 based on vital statistics data. Two findings are noteworthy. First, there was wide variation in opioid prescribing across states. For example, hydrocodone distributions ranged over 12-fold across states, and oxycodone distributions ranged over 7-fold; such variations are noteworthy because, to my knowledge, there is not sufficient data to conclude that the pain need for such medications varies by 7 to 12-fold across the United States. Further, this variation across states was highly correlated with drug poisoning rates; all prescription opioids combined were correlated with drug poisoning deaths at 0.73 for the correlation coefficient, which indicates a high correlation. Investigators reported the total amount of variation, that is, differences between state-level overdose rates and the national average, that was explained by each drug. Note that variance explained is not the same as the risk of overdose, or the proportion of overdose deaths due to a particular drug; rather, it is another way to express correlation. Oxycodone dispensing alone explained 43% of the variation in drug poisoning mortality; methadone dispensing explained 46%. While the death rates from methadone substantially contributed to mortality variation in Paulozzi & Ryan (2006), it should be noted that death rates from methadone have declined precipitously since the time period of the study. Methadone death in the United States reached a height in 2006/2007 at 1.8 per 100,000, and has declined annually since then, stabilizing at 1.0 per 100,001 in 2015-2017, [126] which is a 44% decrease in just one decade. Methadone now contributes a relatively small proportion of drug overdose events, with most recent data suggesting that 14.7% of overdose deaths are attributable to methadone. These declines are attributable to Food and Drug Administration warnings and guidelines for methadone prescribing, as well as voluntary limits on the distribution of high milligram formulations of methadone among manufacturers.[128] Given the declines in methadone use, the findings on methadone in Paulozzi & Ryan (2006) regarding the proportion of variance explained in geographical death rates do not generalize to methadone-related harm in recent years. However, prescription opioid overdose deaths are higher than methadone rates of death and have remained relatively stable in recent years, suggesting that geographic variation explained in prescription opioid overdose deaths is more generalizable than methadone death rates.

Further, Wisniewski et al. (2008)[129] examined the relationship between prescribing of opioids and non-medical opioid use, as well as emergency department visits related to opioids. Data on prescribing were drawn

from the National Hospital Ambulatory Medical Care Survey and the National Ambulatory Medical Care Survey; opioid prescriptions were based on medication codes indicating whether hydrocodone, oxycodone, or a morphine-containing product were prescribed at each patient encounter (including 576,178 patient encounters). Prescription rates increased from 2-fold for hydrocodone, 2.64 for morphine, and 3.21 for oxycodone products from 1995 to 2004. Concomitantly, opioid-related emergency department visits based on Drug Abuse Warning Network (DAWN) data and respondent reports of non-medical opioid use based on NSDUH data increased across the same time period. Correlations between rates of prescription and rates of opioid-related ED visits and non-medical use were significant for hydrocodone (correlations ranged between 0.73 to 0.79) and oxycodone (correlations ranged from 0.76 to 0.87). Taken together, these data indicate strong and statistically significant correlations between opioid supply and opioid-related harm in the US population.

The relationship between opioid supply and opioid-related harm has been examined more recently as well. Ghertner (2019)[130] examined the relationship between opioid sales based on data from ARCOS with county-level opioid-related hospitalization rates based on counties in the states that report data to the Healthcare Cost and Utilization Program (HCUP) program. In a modeling strategy that used variation in Medicare Part D prescriptions as an instrumental variable to increase study rigor, as well as models that controlled for economic factors, there was a 9% increase in opioid-related hospitalizations for each one morphine kilogram equivalent increase in opioid sales. Further, results indicated that each morphine kilogram equivalent in sales resulted in a 14% increase in maternal and neonatal mortality. The relationship was specific to opioid-related hospitalizations, and was not associated with alcohol-related hospitalizations, underscoring the specificity of the association and increasing confidence in the validity of the results. Of note, data from West Virginia were included in the analysis conducted by Ghertner (2019), which analyzed on opioid distributions from ARCOS as well as opioid-related hospitalizations from the Healthcare Cost and Utilization Project. Thus, the findings reported by Ghertner (2019) includes the time frame and geographic distribution of West Virginia and its counties, which supports the opinion that the available data are consistent with a causal role of opioid supply on opioid-related harm specific to West Virginia and the Cabell Huntington Community. In totality, the multiple sources of evidence, cited above, consistently support the high correlation between opioid supply and opioid-related harm.

Further, the consistency of the association across other studies that measure opioid dispensing and sales with opioid related harm and mortality support my opinion that supply of opioids is causally associated with harm.[131] In 2009, Fisher et al. (2013) documented statistically significant and high correlations between the rate of hydromorphone dispensing and deaths due to hydromorphone, as well as the rate of oxycodone dispensing and deaths due to oxycodone. These correlations were high within-province, which is important because the base rates of overdose and dispensing varied by province and yet the correlations remained strong in each. Similar associations with non-fatal outcomes, such as substance abuse treatment admissions, have been published by the same investigators, indicating that the association between prescription opioid supply and opioid-related harms in Canada extends across outcomes related to opioid use disorder, as well as opioid overdose.[132]

The studies cited in the material above are based on associations, and alone are not sufficient in isolation to conclude a casual role of opioid distributions and opioid-related harm. This fact is acknowledged in the discussion section of these publications, however, building a scientific evidence base is not about the conclusion of one paper. I base my conclusion on the totality of evidence from across studies examining a variety of opioid prescribing and distribution measures, opioid-related morbidity and mortality outcomes, across a wide variety of geographic areas. The reliability of the observed association supports the opinion that there is a causal relationship.

The supply of opioids was also facilitated by pharmaceutical promotional activity to physicians. While I did not evaluate the specific marketing materials of the manufacturers, I did evaluate peer-reviewed epidemiological studies that document the association between opioid marketing with sales, which is germane to my expertise. Epidemiological evidence using statistical methods is routinely used to assess the association between exposure to pharmaceutical marketing and sales efforts with changes in prescribing, and has reliably

found across many studies in many populations that exposure to pharmaceutical marketing and sales is significantly associated with increases in prescribing of the marketed drugs. Indeed, available epidemiological evidence using rigorous quasi-experimental designs, such as difference-in-difference models, as well as controlling for numerous potential confounders, has consistently documented an association between the industry payments, meals, sales outreach to physicians, as well as pharmaceutical promotions, with increases in requests to add specific products to hospital formularies[133] as well as increases in rates of prescribing the marketed product.[134–137] These broader literatures provide a consistent evidence base when examining the associations between opioid marketing and opioid sales. Empirical evidence has demonstrated that industry payments to physicians as part of the marketing of prescription opioids were associated with increased opioid prescriptions,[138] and that 1 in 12 physicians in the US, and 1 in 5 family physicians, received opioid-related marketing.[26,138–140] Hadland et al. (2019)[141] used data form the Centers for Medicare & Medicaid Service Open Payments database to assess the monetary value in payments to physicians for opioid products in all US counties over time, as well as data on dispensing of opioids in available counties in the US, and examined the spatial and temporal correlations with prescription opioid deaths as designed in the vital statistics records. The authors used a rigorous statistical model that included controls for a range of county-level factors such as economic environment (e.g., unemployment, income, income inequality), as well as demographics. Results demonstrated that even with statistical controls in place, each one standard deviation increase in payments to physicians was associated with statistically significant increases in prescription opioid overdose, including when marketing was assessed by marketing value in dollars per capita (each standard deviation increase associated with 1.09 times the rate of death), number of payments to physicians per capita (each standard deviation increase associated with 1.18 times the rate of death), and number of physicians receiving marketing per capita (each standard deviation increase associated with 1.12 times the rate of death). Further, these authors conducted mediation analysis to quantitatively demonstrate that the association between marketing to physicians and prescription opioid overdose was mediated by (that is, explained by) the increase in opioid prescribing and increased distribution. However, it is important to note that payments to physicians are only one type of promotional activity, and accounted for only a proportion of the overall promotion strategy for opioid pharmaceuticals. These specific studies do not preclude potential effects of other kinds of marketing efforts; they do however provide empirical evidence for the marketing efforts for which data are available to academic researchers. These results confirm through independent epidemiological analysis that outreach and payments to physicians through the pharmaceutical companies was an important way in which the distribution of opioids across the United States was facilitated.

Finally, Powell et al. (2020)[142] examined the introduction of the Medicare Prescription Drug Benefit (Part D) program in 2006 as a potential driver of opioid use among those aged 65+. This paper is particularly informative given the quasi-experimental design of using an exposure with exogenous variation to assess the effects of changes in opioid use. "Exogenous variation" is a term that is commonly used in epidemiological and economics literature to mean that there is no possibility that confounding factors such as increased prevalence of pain, or increased risk factors for addiction, could explain changes in the exposure. Thus, changes in the Medicare insurance coverage cannot be caused by factors related to use, and for that reason, associations between changes in Medicare and changes in opioid use can be interpreted as causal. Using data from 1999 through 2016, the authors documented that the Medicare insurance expansion affected the opioid use, with states that had a relatively larger proportion of individuals gaining access to prescription drug coverage exhibiting an increase in opioid use based on ARCOS data. Further, the authors examined correlations with drug overdose deaths (specifically those with codes that indicate prescription opioid poisoning), as well as substance abuse treatment admissions (which is an indicator of the occurrence of opioid use disorders). For both prescription deaths and treatment admissions, there was evidence that the increase in the exogenous increase in opioid use caused by the insurance expansion was associated with increases in deaths and treatment admissions; results were robust to a range of sensitivity analyses, alternative modeling of the statistical associations, and a range of quasi-experimental statistical models. These data reinforce the conclusion that opioid use directly affects opioid-related harm, and provide a strong design and test of the hypothesis using the quasi-experimental instrument of changes in Medicare prescription coverage.

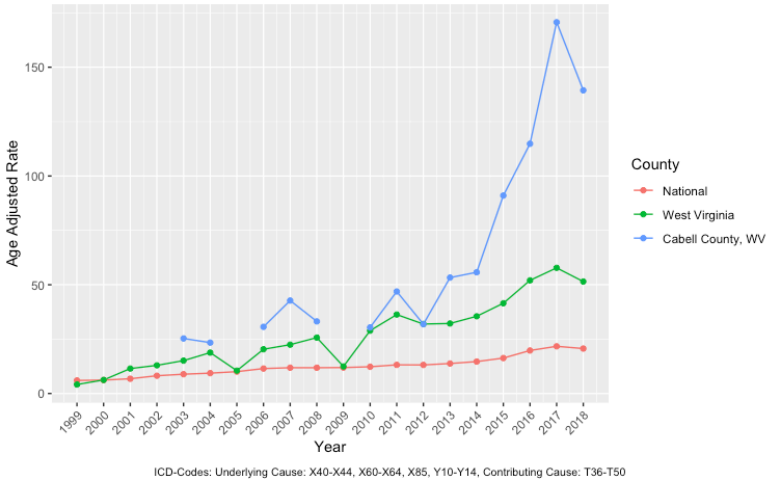
In summary, the available evidence, including temporal and geographic covariance of opioid supply, as well as quasi-experimental changes in opioid availability, strongly correlate with rates of prescription opioid overdose, providing an evidence base to demonstrate that supply and availability of opioids caused an increase in the rate of prescription opioid overdose.

In the sections, below, I provide an overview of opioid-related overdose and other consequences related to opioid use in the Cabell Huntington Community as well as West Virginia as a whole. These sources document an exceptionally high burden of harm in these communities well beyond mortality, including ongoing morbidity from opioid use.

1. Opioid-related harm in West Virginia and Cabell County have increased greatly between 1999 and 2018, including the death rates due to prescription opioids

The National Vital Statistics Surveillance System (NVSS) provides publicly available county-level data on death, allowing for a quantification of the risk of overdose death in Cabell County in years where deaths are sufficient to report without violating data suppression requirements. The data provided by the NVSS are consistent with other sources of data that I reviewed regarding overdose in West Virginia and Cabell County; I rely as a principal source of my opinions the NVSS data given that they are routinely used for epidemiological surveillance. Of particular relevance are trends in opioid-related deaths in West Virginia as a whole and Cabell County in particular. The death rates from 1999 through 2018 for: drug-related death, opioid-related death, and prescription opioid death from the vital statistics records are shown in Figure 3 (note, data from Cabell in 2005 and 2009 are excluded due to data suppression requirements), Figure 7, and Figure 8. These figures are based on my own analysis of the vital statistics data, and were produced using the publicly available age-adjustment, with adjustment provided by the CDC (adjusted based on 2000 census).

Figure 3. Overdose death rates, all drugs

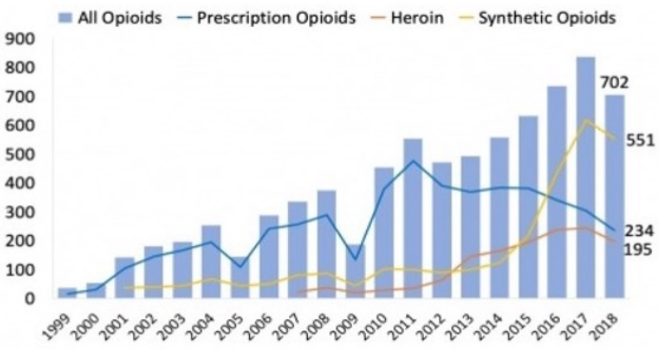


Data suppression. I use publicly available mortality data accessed through the NVSS, specifically the CDC Wonder Multiple Cause of Death 1999-2018 database. Death counts and corresponding rates are suppressed for sub-national data representing zero to nine deaths, as the relatively small size of these estimates may yield unreliable inference. Throughout I will note in figures and text when data are "suppressed" per these CDC reporting and data dissemination guidelines.

(a) Rates of opioid-related harm in West Virginia have largely been increasing since 1999.

Rates of drug overdose. The age-adjusted rate of drug overdose in West Virginia has increased from 4.15 per 100,000 to 51.47 per 100,000 from 1999 through 2018. West Virginia is the state with the highest age adjusted death rate from opioid over this time period. In terms of absolute deaths, from 1999 to 2018 there have been a total of 9,185 drug overdose deaths in West Virginia. Figure 6 shows the map

Figure 4. Number of overdose deaths involving opioids in West Virginia, by opioid category (Source: CDC WONDER, graph generated and published the National Institute on Drug Abuse)

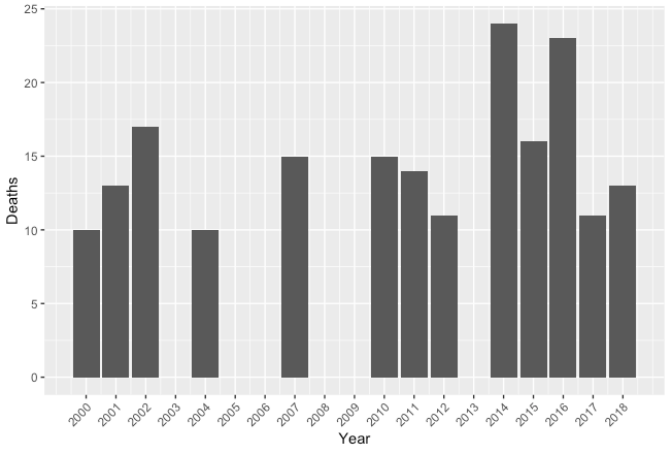


of West Virginia drug overdose deaths in 2014-2018. The blue color of the map becomes darker as the overdose rate increases. Cabell County is the darkest color of blue, indicative of the fact that Cabell County has the highest overdose rate in the state.

Rates of opioid overdose. Deaths in West Virginia that were adjudicated as due to opioids have also increased, from 1.55 per 100,000 in 1999 to 42.06 per 100,000 in 2018, with some evidence of non-linear variation in the years in between. Indeed, from 1999 to 2018, there have been a total of 7,462 opioid overdose deaths in West Virginia. In terms of per capita rates, compared to the national average, West Virginia has had the highest rate of opioid overdose in the country from 1999 to 2018, indicative of substantial harm as the epicenter of the opioid crisis.

The available evidence indicates that there were distinct contributors to the increase in overdose in West Virginia. From 2001 to 2015, prescription opioids were the largest contributor to the increase in overdose deaths over other opioids such as heroin. Figure 4 provides the number of drug overdose deaths in West Virginia across three categories: prescription opioids, heroin, and synthetic opioids other than methadone, by year, from 1999 through 2018. These categories are not mutually exclusive; deaths for which more than one drug was listed were counted in each category; thus the category totals represent counts of events of drugs, and do not sum to the total number of deaths. Data are sourced from CDC WONDER and the graph was generated and published by the National Institute on Drug Abuse.[143] As is clear from the graph, prescription opioids were listed more often than heroin or synthetic opioids as involved in overdose death from 1999 through 2015. In recent years, heroin deaths have increased as being involved in overdose deaths, beginning in approximately 2012-2014; my analysis of the CDC WONDER data indicated that in 2016 to 2017, heroin was counted as contributing to overdose 235 and 244 times in West Virginia (as an important note, the listing of heroin does not preclude prescription opioids from also being involved, again, as these categories are not mutually exclusive). Synthetic opioid (e.g. fentanyl) deaths began exponentially increasing as having involvement in overdose deaths in recent years as well. Of note, increases in heroin and fentanyl deaths are a result of the increase in prescription opioid use in the United States to the extent that prescription opioid use is concurrent with, or temporally prior and causally related to subsequent heroin and fentanyl use. As I detail in Section I, there is sufficient evidence to conclude that prescription opioid use is a cause of heroin and fentanyl use, and approximately 70-80% of individuals who began using heroin in the last 20 years started with prescription opioids.

Figure 5. Number of suicide deaths involving any opioid, West Virginia



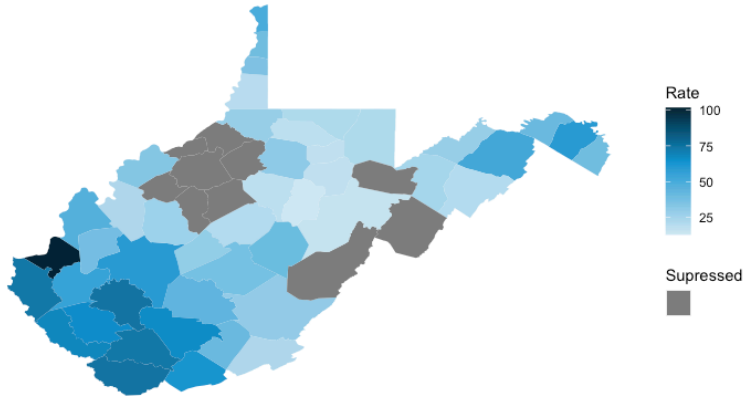
Rates of prescription opioid overdose. To estimate the rate of prescription opioid overdose, I used ICD-10 codes including X40-X44, X60-X64, X85, Y10-14, and T-codes T40.2 and T40.3, as well as a portion of deaths from T40.4. Other analyses of prescription opioid overdose death vary in the codes that are included and the drugs included; T40.2 includes semisynthetic opioids and methadone, as is reported in the literature.[3] Prior to 2013-2015, it was also common to include T40.4 (synthetic opioids) as a prescription opioid death; after 2013-2015, the increase in illegally manufactured fentanyl-related deaths increased in the US, and separating deaths due to prescribed fentanyl from illegally manufactured fentanyl adulterated in the drug supply became difficult to discern. Specifically, T40.4 refers to synthetic opioids, which include highly potent opioids such as fentanyl. Available evidence from the CDC indicate that in approximately 2013-2015,[144] illegally manufactured fentanyl began to be detected in illicit drug supply, leading to exponential increases in overdose death. Thus, after 2013-2015, the deaths included in T40.4 include a mix of overdose due to prescription synthetic opioids as well as those that are due to illegally manufactured and sold synthetic opioids. Given the evidence that illegally manufactured synthetic opioids began contributing to overdose death in the US around 2013-2015, I included all overdoses due to synthetic opioids prior to 2013 as prescription opioid overdose deaths. Then, I estimated the rate of synthetic opioid overdose deaths from 1999 to 2012, and applied that rate to synthetic opioid overdose deaths from 2013 and onwards as an estimate of the number of synthetic opioid overdose deaths that are reasonably attributable to prescription opioids. Deaths that are attributable to prescription opioids have increased in West Virginia since 2000, increasing from 2.05 deaths per 100,000 to a height of 28.24 per 100,000 in 2011. These underlie a high absolute number of deaths attributable to prescription opioids in West Virginia, including 27 in 1999 and 524 in 2011. Similarly to the trend for all opioids, prescription opioid death in West Virginia was substantially higher than the national average before 2015. For example, prescription opioid death in West Virginia ranged from 1.03 times the national average in 1999 to 5.20 times the national average in 2011.

Opioid-related suicide. Suicide using opioids is an additional source of harm that has impacted mortality in West Virginia. Suicide generally refers to intentional self-harm that results in death, and requires a designation of the intentionality of the decedent by the death certificate certifier. In the case of opioid overdose, whether the overdose was intentional or not can be difficult to determine. Suicide may be the designated cause if there is confirmatory evidence such as a suicide note that describes the intentionality, acute suicidal behavior proximal to the death, or other indicators based on investigation. Suicide using opioids has more than doubled in the United States from 1999-2014, from 0.3 per 100,000 to 0.7 per 100,000.[145] In West Virginia the count of suicides due to opioids from 2000 to 2018 from vital statistics is provided in Figure 5. Data on suicide using opioids for some years is not provided in the public vital statistics data due to small numbers. Data indicate the number of suicide deaths that were designated to be attributable to opioids, in years for which data are provided, ranged from 10 in 2000 and 2004 to 24 in in 2014.

(b) Rates of opioid-related harm in Cabell County have also increased since 1999.

Rates of drug overdose. Per the CDC WONDER data, the age-adjusted rate of drug overdose in Cabell County has increased from 25.30 per 100,000 in 2003 to 139.39 per 100,000 in 2018. These rates comprise a high degree of harm; indeed, overall from 1999 to 2018, 836 mortalities in Cabell County have been recorded in NVSS due to drug overdose. Compared to the national average, Cabell County has substantially higher rates of drug overdose per capita, although the absolute number of deaths is indicative of a high burden of harm, with 115 overdose deaths in 2018 alone. Indeed, across all counties in the United States with sufficient data to estimate rates, Cabell County has been in the top 10 counties with the highest rates of drug overdose in all 4 of the last 4 years.

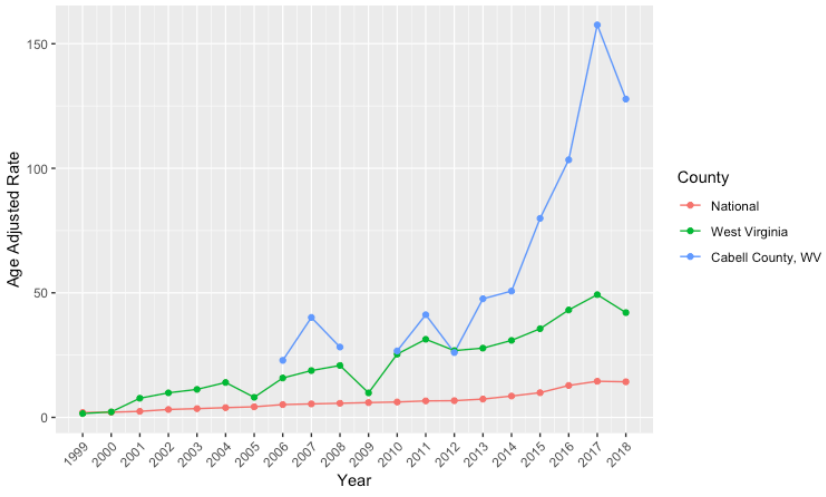
Figure 6. Overdose deaths, crude rate per 100,000 population, 2014-2018, West Virginia



ICD-Codes: Underlying Cause: X40-X44, X60-X64, X85, Y10-Y14, Contributing Cause: T36-T50

Rates of opioid overdose. Per the CDC WONDER data, deaths in Cabell County that were adjudicated as due to opioids have also increased substantially, and Cabell County remains among the counties in the US with the highest burden of opioid overdose death. From 2006 to 2018, the death rate more than quintupled from 22.89 per 100,000 to 127.80 per 100,000. The number of opioid overdose deaths reported in CDC WONDER in Cabell County have increased from 21 to 105 from 2006 to 2018. The rate per capita in Cabell County was between 3.88 and 10.86 times higher than national average in all years for which data are available; the heightened risk compared to the national average peaked in 2017 with a rate of opioid overdose that was 10.86 times the national average. Much like West Virginia, opioid overdose death in recent years has increased in recent years concomitant with heroin overdose and high-potency synthetic opioids, which are attributable to individuals who also use or have used prescription opioids to the extent that prescription opioids were temporally prior to and caused subsequent heroin and synthetic opioid use. The available literature cited in Section I indicate that approximately 70-80% of individuals who began using heroin in the last two decades first used prescription opioids, indicating that a similar proportion of deaths due to heroin and synthetic opioid use are attributable to prescription opioids.

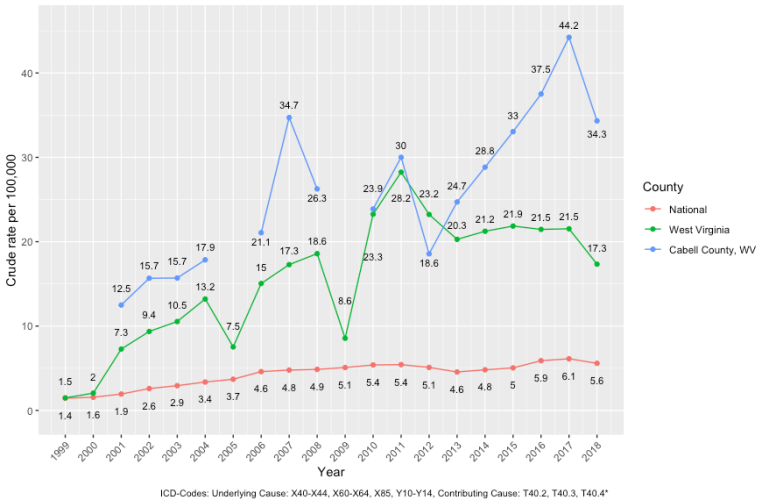
Figure 7. Overdose death rates, all opioids



ICD-Codes: Underlying Cause: X40-X44, X60-X64, X85, Y10-Y14, Contributing Cause: T40.0-T40.4

Rates of prescription opioid overdose. Deaths that are categorized as prescription opioid related (T40.2, T40.3, and a portion of T40.4 as described above) were higher in Cabell County compared with both West Virginia and the national average for the years in which available NVSS estimates are released. In total from 1999 to 2018, the CDC reports on 401 deaths attributed to these prescription opioids in Cabell (note that some years are not included in this estimate due to small numbers in particular years), per my estimate including the proportion of synthetic opioid overdose deaths that are reasonable attributable to prescription opioids based on rates prior to illicitly manufactured synthetic opioids began to be detected in the drug supply. While data are suppressed for certain years in the publicly available vital statistics data, for years in which data are available, these prescription drug overdose deaths increased from 12.50 deaths per 100,000 in 2001 to a height of 44.23 per 100,000 in 2017. These rates are indicative of a large degree of burden. In Cabell County, prescription opioid overdose deaths are substantially higher than the national average for the years in which reliable estimates for Cabell County could be extracted from NVSS; the heightened risk compared to the national average peaked in 2007 with a rate of opioid overdose that was 7.26 times the national average.

Figure 8. Overdose death rates, prescription opioids



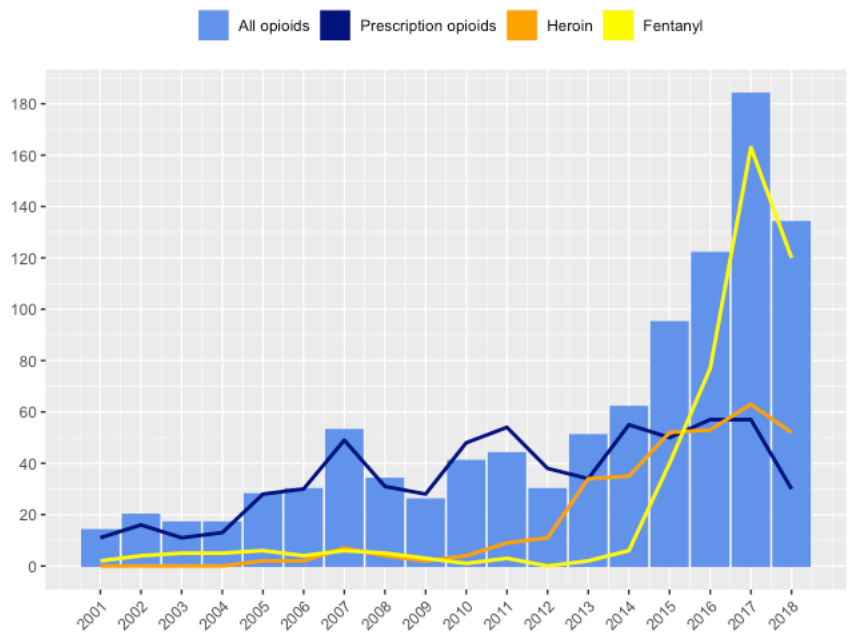
Opioid-related suicide. Suicides using opioids occur in Cabell County, adding to the public health burden of the opioid epidemic. However, suicide using opioids is relatively rare and not reported with a frequency that allows a statistical analysis.

Rates from the Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research (WONDER) database are consistent with local sources of data collection and surveillance. The rates of drug overdose provided by NVSS are consistent with numerous other sources from the local community and State that I reviewed in the process of assembling this report. I reviewed data from the West Virginia Health and Human Resources Bureau for Public Health, which regularly releases information on drug overdose and related harms across numerous jurisdictions in West Virginia. These sources converge but do not completely overlap with data that are released by NVSS, due to differences in the deaths that are included between those who died but did not live in the Cabell Huntington Community, and other validation and synthesis procedures that are done through vital statistics as outlined in CDC publications.[146] The data from the West Virginia Health and Human Resources Bureau for Public Health as well as local sources that have been produced all converge in indicating that prescription opioid overdose deaths were the primary source of overdose deaths in the first stages of the epidemic, from the late 1990s through approximately 2010.

These sources of data indicate that the overdose crisis in West Virginia, and the Cabell Huntington Community, began with prescription opioid overdose deaths and then transitioned to heroin and synthetic opioid overdose deaths. In West Virginia as a whole, for example, from 2001-2011 the state reported just 129 heroin-related deaths, compared to 1,859 deaths during the same period for a composite of codeine (N=54), hydrocodone (N=485), hydromorphone (N=34), morphine (N=243), oxycodone (N=619), oxymorphone (N=205), propoxyphene (N=129) and tramadol (N=82). There were also 259 fentanyl-related deaths from 2001-2011, which would increase the prescription drug-related deaths to 2110 from 2001-2011, assuming that the illicit fentanyl wave did not occur until 2013 and later, so that the fentanyl deaths before that time were associated with prescription drugs (e.g. Duragesic). In Cabell County, available local data indicate that at least one prescription opioid was listed as involved in overdose deaths throughout most of the last two decades. Figure 9 provides the total number of overdose deaths in Cabell County, with data drawn from the exhibit to

the report of Gordon Smith, MD. I used these data to recreate the data visualization provided by NIDA as reported in Figure 9, subset to Cabell County for the years 2001 to 2017. The figure reports the total number of opioid overdose deaths, as well as the number that are related to prescription opioids (codeine, hydrocodone, hydromorphone, buprenorphine, methadone, morphine, oxycodone, oxymorphone, and tramadol), heroin, and fentanyl. Of note, these the drugs contributing to each death are not mutually exclusive. Based on these data, there were substantially more overdose deaths for which at least one prescription opioids was listed as involved in all years prior to 2011; from 2011 to 2015, there were similar number of deaths listed as involving prescription opioids and heroin, and after 2015, heroin and fentanyl became more modally listed on death certificates, although prescription opioids remain a strong contributor as well. Indeed, it is worth highlighting that there were *zero* deaths from heroin in 2001, 2002, 2003, and 2004. Across those years there were 68 overdose listings of at least one prescription opioid a contributing factor. From 2005 to 2011, heroin deaths remained relatively rare, ranging from 2 to 9, while during the same time there were a minimum of prescription opioid were listed 22 times for a total of 227. Prescription opioid deaths continue to contribute significant harm in Cabell County, listed an additional 255 times from 2012 to 2017. These trends are consistent with multiple sources of local data that have been provided to me for review.[147,148] Of note, heroin and fentanyl, consistent with national data sources, have increased the public health burden in the Cabell Huntington Community. It is worth underscoring that the available information indicates that most individuals who use heroin and other synthetic sources transitioned to these sources from initiation with prescription opioids, which are easier to obtain and involve routes of administration with less stigma than heroin. National and State sources are also consistent with other local data that has been collected and synthesized across numerous sources documenting the geographic distribution, increases in deaths, and attribution of deaths to prescription opioids as well as heroin and synthetic opioids.[149]

Figure 9. Cabell county overdose deaths by drug type 2001-2018



2. Because of limitations and gaps in existing surveillance sources, rates of harms based on those sources are underestimates.

Important in interpreting the death rates attributed in the vital statistics system to prescription opioids are a number of limitations. Designation of opioid-related harm in the CDC WONDER data due to overdose is complicated by the heterogeneous ways in which death certificates are completed across jurisdictions. The designation of an opioid-related death in CDC WONDER is assessed statistically with "T-codes" found in the ICD-10, to identify the drug(s) involved; however, these codes are inconsistently used and applied. The publication by Slavova et al. (2015)[10] details the methodological issues with respect to counting overdose cases using death certificates and T-codes. However, it is worth noting that the high-quality procedures conducted to investigate and designate overdose deaths in West Virginia have been extensively documented. Drug overdose death data have been reviewed and maintained by the West Virginia Department of Health and Human Resources Bureau for Public Health along with the Office of the Chief Medical Examiner with examination of toxicology results and investigations as reported on death certificates since at least 2001.[11]

Further, as outlined in reports and peer-reviewed publications,[11–13] the West Virginia Office of the Chief Medical Examiner created a forensic drug database in 2005 to track and record information on overdose. Overdose deaths are designated based on forensic investigation and pathology, including toxicology and autopsy, preceded by drug screening which is conducted in all medical examiner-referred deaths. Toxicology is then confirmed through tissue sampling with high-quality and high-validity tests for the presence of a wide range of opioids. Thus, while vital statistics estimates may underestimate specific causes of death related to prescription opioids, they provide a reliable source of information regarding opioid-related harms, especially in these counties.

3. Polydrug use at toxicology in drug overdose: implications for causal attribution.

Available evidence from national epidemiological studies, as well as confirmed via local data including West Virginia public health reports, indicates that in the early days of the epidemic around the mid to late 1990s, opioid overdose deaths primarily involved prescription opioids,[150] frequently without the presence of other drugs. For example, as recently as 2010, analyses of death certificates indicated that among drug overdose deaths involving pharmaceuticals, opioids were the most frequently implicated drug listed, and of deaths involving psychotherapeutic and central nervous system pharmaceuticals, opioids were the single class of drugs in 30% of cases.[151] As the epidemic progressed towards the second and third stages, in which heroin and high-potency synthetic opioids as a cause of death significantly increased as contributors to the overdose death causes, polydrug use on toxicology became more frequent in the majority of drug overdose deaths involving opioids.

Given that the prevalence of multiple drugs listed on death certificates involving opioid overdose has increased, it is critical to note that deaths in which prescription opioids are listed, even in the presence of multiple other drugs listed, are attributable to prescription opioids through drug-drug interactions. That is, there is substantial epidemiological, toxicological, and clinical literature that indicates that the adverse respiratory depressant, seizure, and other consequences of opioid use are accelerated and exacerbated when other drugs are present,[150,152–155] so much so that guidelines warn against prescribing a variety of medications such as benzodiazepines with opioids.[156,157] The mechanisms underlying these interactions include through inhibiting metabolism as well as other pathways.[158] The most common drugs that in conjunction cause drug overdose include opioids and benzodiazepines, often in combination with alcohol. While benzodiazepines alone rarely cause overdose death,[159] they potentiate harm when used in combination with other drugs such as opioids. Other drugs that are prevalent in toxicological screening when overdose occurs in conjunction with opioids include skeletal muscle relaxants,[160] cocaine and other stimulants such as methamphetamine, as well as tranquilizers and other depressants. In cases of drug-drug interaction, the opioid was a necessary component cause of the overdose death.[161] That is, without the opioid present, these deaths would not occur. The addition of other drugs such as benzodiazepines potentiates the overdose potential of the opioids; indeed, given that benzodiazepines alone rarely cause death, cases in which opioids and benzodiazepines are present may have been caused by both, but the opioid is a necessary component for death to occur. Available epidemiological literature highlights the extent and damage of drug-drug interactions involving opioids. Tori et al. (2020) documented that from 1999 through 2017, benzodiazepines were present in 33.1% of prescription overdose deaths and alcohol was present in between 9-14% prescription opioids overdose deaths.[162] Thus, deaths in which multiple drugs are listed remain attributable to opioids given the strong evidence of harm and overdose associated with use, and accelerated but not replaced by use of other drugs. Thus, prescription opioids are highly likely to be the most significant contributing cause when listed on death certificates.

F. Increases in neonatal abstinence syndrome, emergency department visits, admissions for treatment, and non-medical opioid use among adults and adolescents are additional key harms due to opioids in the population

Neonatal abstinence syndrome. Neo-natal abstinence syndrome (NAS) occurs when infants are born exposed to opioids in utero and experience withdrawal symptoms after birth. The majority of neonatal abstinence syndrome among US infants is due to opioid exposure in utero.[163] Withdrawal symptoms develop in an estimated 55-95% of opioid-exposed infants, depending on the extent of exposure as well as a range of clinical and demographic predictors, and 30-65% of infants require pharmacological treatment for withdrawal symptoms.[164] NAS is associated with significant medical morbidity, from low birthweight and general discomfort and pain for the infant to medically serious issues such as respiratory disorders and seizures. Cases of NAS can have long-lasting effects on infants, as the clinical literature has documented increased incidence of developmental delays and child behavior problems into childhood.[165] Several large-scale databases have been used to assess trends in NAS, including the Kids' Inpatient Database (KID) and the Nationwide Inpatient Sample (NIS), part of the HCUP family of databases. Available estimates indicate that the rate of NAS per 1,000 hospital births increased from 1.2 in 2000 to 3.39 per 1,000 live births in 2009.[166] An updated publication from the NIS data indicated an increase in NAS from 1.2 per 1,000 in 2004 to 7.5 per 1,000 in 2013 among rural infants, and 1.4 in 2004 to 4.8 per 1,000 in 2013 among urban infants.[167] Further, these data also provided estimates of deliveries complicated by maternal opioid use among delivering mothers, indicating an increase from approximately from 1.3 per 1,000 deliveries in 2004 to 8.1 per 1,000 deliveries in 2013 among rural mothers, and approximately 1.6 per 1,000 in 2004 to 4.8 in 2013 among urban mothers. These estimates are consistent across other data sources. Data from the State Inpatient Databases, also housed in HCUP, documented a 300% increase in the incidence of NAS from 1999 through 2013, from an incidence rate of 1.5 per 1,000 hospital births to 6.0 per 1,000 hospital births in 2013.[168] Thus, these data together show that NAS is dramatically increasing in the United States, because of increases in maternal opioid use at the time of delivery. Children with NAS will require long-lasting monitoring and increased supports through development, long after treatment for NAS and release from hospital care.

Figure 10. Neonatal abstinence syndrome

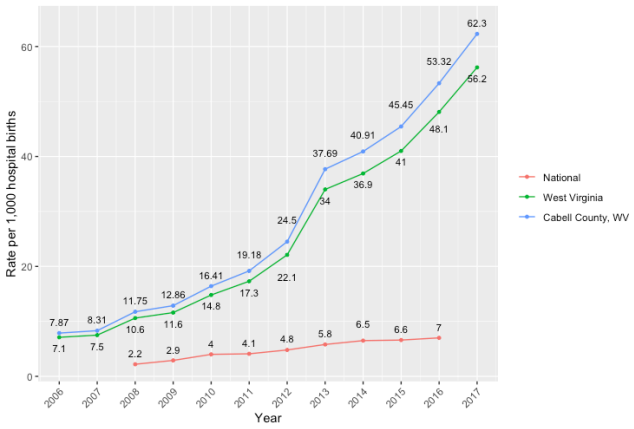
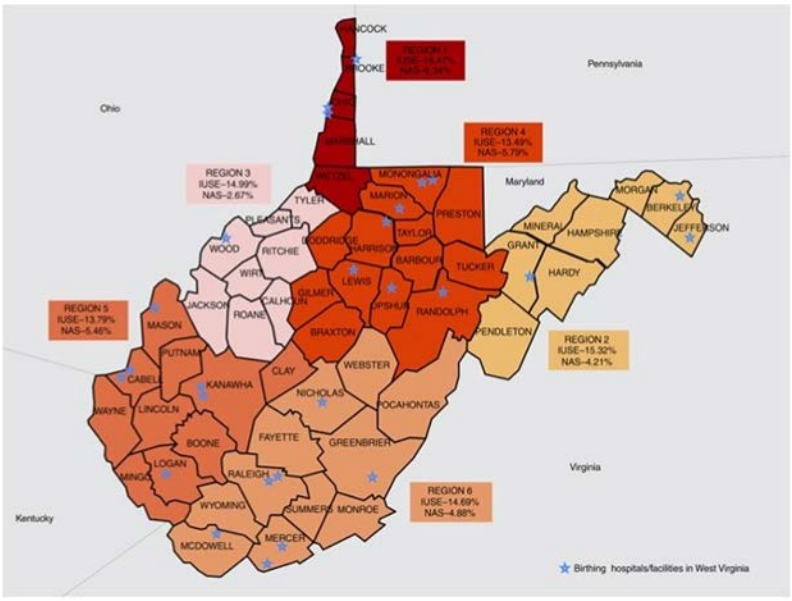


Table 1. Estimated Number of NAS Births in Cabell County	
2006	10
2007	10
2008	15
2009	16
2010	19
2011	23
2012	30
2013	44
2014	46
2015	49

Neonatal abstinence syndrome continues to be a heavy burden in West Virginia and within its counties; it is challenging clinically to treat and remains associated with adverse long-term outcomes.[169–171] As shown in Figure 10, the rate of NAS in West Virginia more than quintupled from 2008 to 2017, from 10.64 per 1,000 births in 2008 to 56.17 per 1,000 births in 2017. These estimates are based on HCUP data from 2007 to 2017, as well as State Inpatient Data from 2006 and 2007. In terms of absolute numbers, in West Virginia there were a total of 18,675 births where the mother's state of residence is West Virginia in 2017;[172] with an NAS rate of 56.2 per 1,000 in 2017, this would indicate approximately 1,050 children with NAS and in need of NAS-related care in West Virginia per year in recent years. Also shown on Figure 10 is the prevalence of NAS in the US as a whole based on the years available in HCUP data, and as shown NAS in West Virginia is always higher than the US as a whole. Data from the West Virginia Department of Health provides additional information on the burden of harm from NAS to infants in Cabell County. Specifically, in 2017, the West Virginia Department of Health estimated the NAS prevalence in Cabell County to be 6.23%, or 1.109 times the rate of NAS in West Virginia

as a whole. Given the evidence that the NAS rate was 1.109 times higher in Cabell County than in West Virginia as a whole, I can estimate the prevalence and number of expected NAS infants in Cabell during the past decade. The estimated prevalence is provided in Figure 10, and the estimated number (prevalence times number of live births) is provided in Table 1. These data are confirmed based on independent collection of surveillance sources. For example, Project WATCH (Working in Appalachia to identify at-risk infants, Critical congenital heart disease, and Hearing loss) has been tracking NAS in near real time in West Virginia,[173] providing sentinel surveillance to improve outcomes, and indicated an NAS rate of 51.3 per 1,000 infants in 2017, which is within the range of what is reported in HCUP data sources. Table 1 provides my estimate of the number of NAS births in Cabell County. Figure 11 provides a map of NAS in West Virginia from Project WATCH, indicating high rates of intrauterine substance exposure (IUSE) as well as NAS throughout West Virginia, including Cabell County, indicative of ongoing harm to the community.

Figure 11. Project WATCH surveillance data on prevalence of intra-uterine substance exposure (IUSE) and neonatal abstinence syndrome (NAS) in West Virginia by SAMHSA sub-state regional classification system, N = 20,002

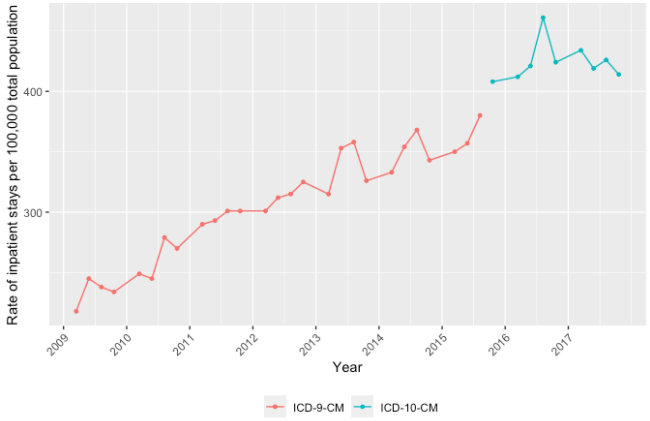


Opioid-related hospital use. Another way to quantify the contribution of opioids to harm in West Virginia, especially in the Cabell Huntington Community is to examine the burden and trends in hospital use, including inpatient, outpatient, and emergency visits. Data are drawn from the HCUP a reliable and well-characterized source of surveillance data in almost all states regarding healthcare use and expenditures. In West Virginia, as shown in Figure 12, opioid-related inpatient hospital stays doubled in less than 10 years, from 218 in the first quarter of 2009 to 434 in the first quarter of 2017.

While data are not publicly available from HCUP on specific counties and cities, available information indicates that the Cabell Huntington Community was significantly affected in terms of opioid-related medical care usage, and that statistics regarding trends in hospital use for West Virginia as a whole likely underestimate the burden of harm that was experienced by the Cabell Huntington Community. For example, for West Virginia as a whole, available data indicate that in 2019, there were 7,922 ED visits related to overdose in West Virginia.[174] At a total population size of 1,792,147, this indicates a crude overdose rate of 442.04 per 100,000.[175] In Cabell County, there were 835 ED visits related to overdose.[174] At a total population size of 91,945, this indicates a crude overdose rate of 908.15 per 100,000,[175] over twice the rate for West Virginia as a whole.

Non-medical opioid use in West Virginia. Data on non-medical opioid use in primarily household populations, both prescription opioid and heroin use, can be drawn from the National Survey on Drug Use and Health (NSDUH), which is conducted annually in the United States and draws a representative sample of a primarily household sampling frame. Understanding the sampling frame is important, because populations with high levels of opioid use are excluded from the sampling frame, such as those incarcerated and homeless. Thus, the

Figure 12. Opioid-related hospital use



NSDUH estimates should be considered an underestimate of the total state burden. With that caveat, available evidence indicates that non-medical pain reliever use (which is primarily opioids) is declining among non-institutionalized mostly household populations in West Virginia overall, from 1.20% of those in West Virginia in the sampling frame reporting past-month use in 2015-2016 to 0.90% in 2017-2018. Drug use disorder, however, has increased; available West Virginia data indicate that 2.40% of those in the sampling frame in West Virginia met criteria for past-year illicit drug use disorders in 2015-2016, which increased in 2017-2018 to 2.90% prevalence.[176] The West Virginia NSDUH report comparing 2016-2017 to 2017-2018[177] indicates that among those 18 and older, the prevalence is increasing, with 2.11% prevalence in 2016-2017, and 2.61% prevalence in 2017-2018.

Non-medical opioid use among adolescents in West Virginia. Data on trends and current burden of opioid use among adolescents in West Virginia can be drawn from two sources, including the NSDUH, as well as the Youth Risk Behavior Surveillance Survey (YRBS), which is also state-level representative of adolescents in schools (and thus, again an underestimate of total burden given that adolescents who drop-out of school are at higher risk for drug use than those who remain in school). In the NSDUH data, evidence indicates that non-medical use of prescription pain relievers has been relatively stable in recent years, from 2.86% to 2.89% in 2016-2017 and 2017-2018, respectively, and reports of heroin use in the past year among adolescents in West Virginia from 0.70% to 0.90% in 2016-2017 and 2017-2018.[177] Data from the YRBS indicates the proportion of adolescents in West Virginia who have *ever* used heroin in their lifetime has increased in the past decade, from 3.0% in 2003 to 3.4% in 2017.[178,179] Further, the proportion of adolescents using drugs through injection has also slightly increased, from 2.3% in 2003 to 2.5% in 2017.[178,179] Thus, YRBS data capture a much higher estimate of heroin use among WV adolescents. This indicates a high degree of continued harm to the community, especially given the risk of blood-borne infection transmission through needle sharing among adolescents injecting drugs.

Other opioid-related harms in the Cabell Huntington Community. In 2016, the most recent year of available data, the Mayor's Office of Drug Control Policy estimated 1,476 emergency calls reporting an overdose in Cabell County;[180] each of these calls represents one incident and may include multiple individuals if they were in the same location. Further, the number of overdose emergency calls is an underestimate of the total number of non-fatal overdoses. While the total number of non-fatal overdoses is difficult to empirically quantify, a study based on medical records of 9,940 insured individuals who received 3+ opioid prescriptions within 90 for noncancer pain found that the rate non-fatal to fatal overdoses was approximately 7 non-fatal overdose for each fatal overdose.[181] Given that there were 132 fatal overdoses in Cabell County in 2017, I estimate that at least 924 individuals experience at least one non-fatal overdose in Cabell County in 2017 (at least 2-3 individuals per day), a ratio that is likely to be similar in other years as well. This number of non-fatal overdoses is a number that is certainly a conservative underestimate given that overdose has increased with the adulteration of the drug market with highly potent synthetic opioids.

Other harms due to opioids to adults in Cabell County include the wide range of medical and psychiatric disorders that are concomitant as a result of opioid use. The Mayor's Office of Drug Control Policy indicates that blood borne diseases associated with injection drug use are increasing in Cabell County;[182] for example, the incidences of Hepatitis B and C were 10.1 per 100,000 and 3.4 per 100,000, respectively, in West Virginia. Applying these incidence rates to the adult population of Cabell County, I estimate that each year in Cabell County there are approximately 75 new cases of Hepatitis B and 25 new case of Hepatitis C. These in coupling with the array of other medical and psychiatric conditions that co-occur with opioid use disorder indicate a heavy burden to the community.

G. Finally, endocarditis and other infections that are associated with heroin and other opioid use are life threatening and evidence indicates that they have been increasing in frequency in West Virginia as the opioid crisis has unfolded across the last decade. Endocarditis includes an infection of the heart chambers or valves and can be caused by bacteria and other germs through injection. In West Virginia, evidence indicates that endocarditis continues to be a serious issue that strain the community and the medical system. For example, data from the Charleston Area Medical Center was used to examine admissions for endocarditis from 2008 to 2015, and documented a dramatic increase in the number of admissions for endocarditis within the medical system, from 26 documented cases in 2008 to 66 in 2015, and resulting in over $13 million dollars in losses to the medical system.[183]Need for treatment in the Cabell Huntington Community

There is need for treatment and recovery services for opioid use disorder across the country, with many communities struggling to scale up capacity and providers with sufficient training in order to meet demand.[184–187] Understanding the total needs for treatment in the Cabell Huntington Community is another metric of the harm to communities for the continued opioid crisis. I provide some conservative estimates of the need for treatment in this section, as well as information on the needs of services for families and children. Of note, there are a range of current services that are provided in the Cabell Huntington Community that aim to provide treatment services to individuals with OUD, including emergency services, inpatient and outpatient OUD recovery, peer support, MOUD, services for women and families, and neonatal care. These have been described to me in meetings with local city and county officials (e.g. Jan Radar, City of Huntington Fire Chief, Rocky Johnson, City of Huntington Police Department) as well as addiction providers and researchers (e.g. Todd Davies, Marshall University Assistant Professor, Beth Walsh, Marshall University Associate Director of Operations for Addiction Sciences in Family Medicine, Stephen Petrany, Chair of Family & Community Health, Marshall University School of Medicine, David Chaffin, Professor, Marshall University). The consensus among local officials and experts is that while the community provides services for those affected by OUD, they are insufficient because of the magnitude of the public health issue. Thus, in this section I provide my estimate of the total treatment needs, and note that my discussion with local officials and experts indicate that these needs are insufficiently met by current treatment and service availability.

Number of individuals with opioid use disorder. I estimated the number of individuals with opioid use disorder (OUD) in the US, West Virginia, and Cabell County in order to obtain an estimate of the number who should have access to services to treat OUD, under the assumption that any individual who has mild, moderate, or severe OUD may have significant symptoms of discomfort, withdrawal, and additional distressing and medically-serious symptoms upon reduction or discontinuation use, and thus should have accessible and available services in a medically supervised way through appropriate evidence-based treatment. Of note, this estimate of OUD numbers is an underestimate of the total number of individuals who may need medically supervised resources to manage reduction or cessation of opioid use, including those who use opioids in medically-supervised settings who may have tolerance to medication and experience withdrawal upon cessation given that continued opioids use and reductions in use often require additional medical supervision and can be associated with morbidity and mortality even in the absence of meeting criteria for OUD.

Estimating the number of people with opioid use disorder is a challenge given that there is no systematic way to count this population. However, we can rely on a variety of data sources that inform epidemiologically regarding the plausible range of dependent or regular opioid users in a given area. A well-accepted method in epidemiology for many years for estimating population sizes for difficult to count groups to use multiplier methods: divide the known rate of an outcome for the difficult to count group by the number of individuals in the population of interest with the outcome to estimate the size of the difficult to count group. For individuals with OUD, available systematic review and meta-analyses have estimated the overdose mortality rate of individuals who are ascertained as having OUD, in treatment for OUD, or otherwise can be reasonably assumed to experience OUD based on duration and extent of opioid use. The most recent meta-

analysis was published in 2019 in JAMA Psychiatry,[188] among the most prestigious and high-impact journals in the field. This systematic review included 124 cohort studies that assessed mortality rates among 'extramedical' opioid users (defined as "use of heroin or other illicitly manufactured opioids and the use of pharmaceutical opioids outside the bounds of a medical prescription"), including 56 that assessed drug overdose rates, and of those, including 6 studies that were conducted within the United States. The meta-analysis included samples of individuals with heterogeneous underlying inclusion criteria, including community-based studies of individuals using opioids, those in treatment for opioid use disorder (including residential treatment, methadone maintenance and other medications for opioid use disorder (MOUD)) and individuals utilizing other kinds of medical care for ongoing medical need related to opioid use. Note that among the studies included in the meta-analysis, there were no studies that specifically focused on mortality rates among those using opioids only as prescribed within medical supervision (see Appendix 5 of Larney et al.), although the inclusion criteria do not preclude individuals who used opioids in this way if they, for example, underwent detoxification or OUD treatment, thus it is important to underscore that the estimate of the size of the OUD population in Cabell may be an undercount of those who may have symptoms of OUD but have not been ascertained in the specific inclusion criteria of the meta-analysis. The common linkage was history of non-medical opioids use or dependent use of opioids. However, individuals who use opioids medically at high doses for sustained periods of time often develop painful withdrawal and craving during cessation of use,[189,190] which in many cases calls for increased services including opioid substitution therapy, as well as other opioid-related services as necessary.[191,192] The estimated overdose death rate, averaged across all studies, was 0.52 per 100 person-years, with a confidence interval from 0.46 to 0.59 per 100,000. When examined just among those studies conducted in the United States, the range of drug overdose death rates was comparable to the overall rate, ranging from 0.21 per 100,000 to 0.61 per 100,000, thus estimation was done with the overall meta-analyzed drug overdose rate of 0.52 per 100,000. Given an event rate of 0.52 per 100,000, we can estimate the number of people who have OUD if we know the number of drug overdoses in a particular area, and divide that number by 0.52 per 100,000, to provide an estimate of the OUD population.

Note that Larney et al. examined the risk for all overdose deaths regardless of the drug that caused the overdose (the majority of the overdose deaths among individuals with OUD include opioids, but other drugs may cause or contribute to opioids when used contemporaneously);[193] thus, the rate of 0.52 per 100,000 would include overdose deaths from opioids, as well as other drugs. To summarize, 0.52 per 100,000 is the overall overdose death rate among those with OUD; thus, dividing the number of total overdose deaths (including but not limited to opioids) by 0.52 per 100,000, I obtain an estimate of the size of the population with OUD.

However, the application of the 0.52 per 100,000 estimate needs to be adjusted for the increase in the death rate that occurred after fentanyl adulteration. The studies included in the Larney et al. study were published before the outbreak of fentanyl-induced deaths, so the estimated overdose death rate of 0.52 per 100,000 is likely an underestimate of the total mortality risk among those with OUD. Therefore, it is appropriate to apply a correction to the estimate in Larney et al. Specifically, that the estimated overdose event rate from synthetic opioid use is approximately three times that of heroin based on available literature (the overdose rate due to heroin and synthetic non-methadone opioids increased by a factor of three from 2011 to 2015).[194,195] With the available evidence regarding the proportion of overdose deaths that are due to synthetic opioids versus other drugs, I applied a death rate three times higher than what is reported in Larney et al for the proportion of cases that is attributable to synthetic opioids. In 2018 in Cabell County, approximately 84% of the overdose deaths were due to synthetic opioids (compared to, for example just 10% in 2013, the year before the fentanyl crisis began) based on publicly available vital statistics data.

In Cabell County, the number of drug overdoses in 2018, the most recent year of available data, is 115, and an estimated 84% of those deaths are attributable to synthetic opioids. Thus, assuming a death rate of 0.52 per 100,000 for 16% the underlying population of opioid users and a death rate of 1.56 among 84% of the underlying population individuals with OUD, I estimate that there are approximately 8,252 individuals who have OUD in Cabell County, who may be in need of treatment services. Using the confidence interval provided by Larney et a. (2019), we can estimate a plausible range of the number of individuals who have

OUD as 8,186 to 8,309. There are an estimated 93,224 people in Cabell, thus this estimate indicates that the prevalence of OUD in Cabell County is approximately 8.9%.

It should be noted that even an estimate of 8-9% prevalence is likely an underestimate, given that Larney et al. reports on death rates among "extramedical" opioid users. In 2017, 106.8 opioid prescriptions were dispensed for every 100 people in Cabell County based on IQVIA estimates provided by the CDC.[196] Even among those who are prescribed opioids who do not concurrently or subsequently use non-medically, credible reviews and meta-analyses suggest that approximately 8-12% of individuals who use opioid analgesic prescriptions for prolonged periods of time will develop moderate to severe opioid use disorder, and 21-29% will develop mild to severe disorders.[62]

It is accepted epidemiologic practice to base projections on reasonable inferences from the data, especially where multiple data sources and analytic methods are employed. I reviewed the estimates of prevalence of OUD in the Cabell Huntington Community with scientific experts in the area to determine whether the estimates that I generated were consistent with other sources of data. Indeed, the estimates that I generated are highly credible with local sources. Todd Davies, the Associate Director of Research Development in the Division of Addiction Sciences at Marshall University has collected and analyzed data on the estimated prevalence of OUD in the Cabell Huntington Community.[197] In the Cabell Huntington Community, approximately 7,581 unique individuals considered to have current diagnoses OUD within the care systems for which data is available, and an additional 8,137 with multiple failed drug screens, which is consistent with underlying OUD.[198] These diagnoses are an underestimate of the total OUD population given that they represent those that came to clinical attention. These estimates are remarkably within the range of the estimated OUD prevalence per my analysis, suggesting that it is highly credible based on multiple sources of evidence to place the prevalence of OUD in the Cabell Huntington Community of at least 8-9%, based on two independent data sources. I estimate the prevalence of at least 8-9% because both analyses underestimate the total OUD population. Thus, independent sources of data collection and analysis came to the same general estimate, providing support for the validity of the estimation process.

Number of individuals with opioid use disorder across time. Based on the methodology above, I can estimate the total number and prevalence of opioid use disorder in the US, West Virginia, and Cabell Huntington Community by year. By way of summary, I used the death rate among individuals with OUD from the most recent meta-analysis of cohort studies in order to anchor my estimation the best available literature. This meta-analysis includes a number of cohorts that are based in the US and North America, and estimates are generalizable. I made an additional modification to the estimates in order to examine prevalence data across time, based on higher death rate from opioids that is commensurate with the adulteration of the opioid supply with high-potency synthetic opioids. Specifically, for each year, I estimated the proportion of overdose deaths in which synthetic opioids were listed as a contributing cause. I then weighted each year for the higher death rate from synthetic opioids that would be expected. That is, an individual using non-synthetic opioids has a lower risk of death given each use than an individual using high-potency synthetic opioids. The meta-analytic estimate provided by Larney et al. (2019) is based on cohorts prior to the introduction of high-potency synthetic opioids into the opioid supply, thus the death rate from opioids is likely lower in the meta-analysis than in recent years

Figure 13. Prevalence of opioid use disorder in the United States, West Virginia, and Cabell County

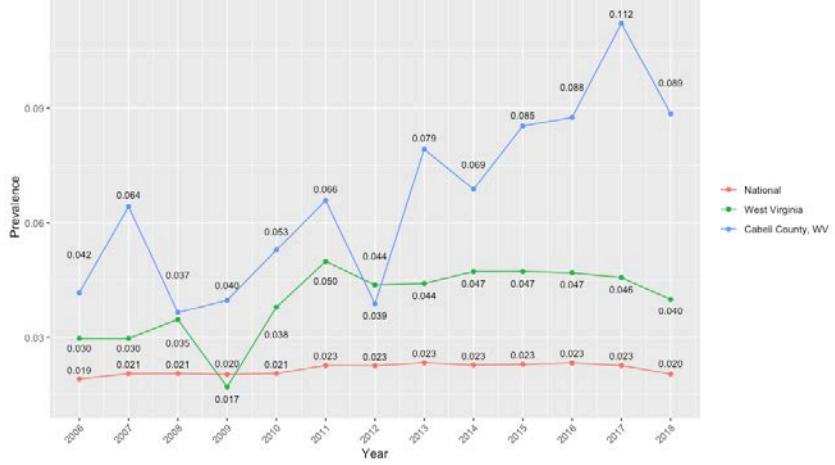


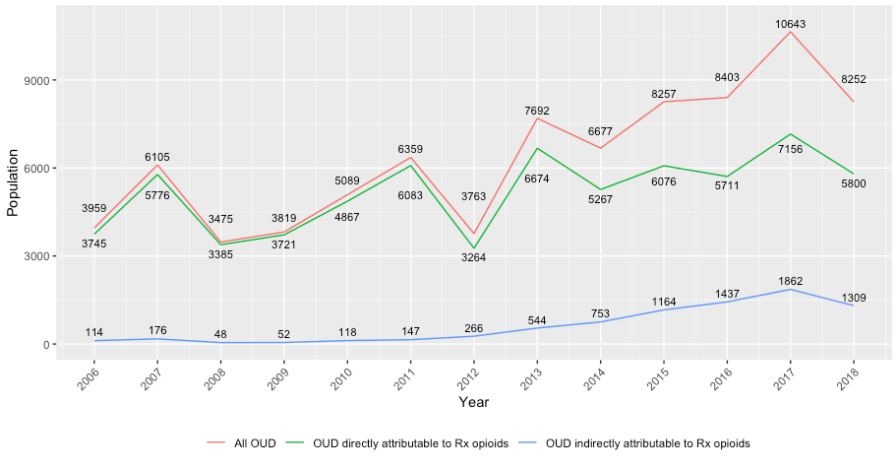
Table 2. Estimated number of individuals with OUD in the US, West Virginia, and Cabell County

	US	West Virginia	Cabell County
2006	5,700,763	54,387	3,959
2007	6,177,370	54,533	6,105
2008	6,249,141	63,824	3,475
2009	6,236,336	31,494	3,819
2010	6,347,812	70,330	5,089
2011	7,093,750	92,512	6,359
2012	7,122,596	81,148	3,763
2013	7,412,955	81,803	7,692
2014	7,292,649	87,375	6,677
2015	7,406,957	87,139	8,257
2016	7,552,707	85,859	8,403
2017	7,415,786	82,880	10,643
2018	6,673,870	72,200	8,252

of opioid users. Therefore, I adjusted each estimate for the death rates of synthetic and non-synthetic opioids to provide a more accurate total estimate of the number of opioid users. Adjustments for death rates and extrapolation from meta-analyses to estimate population sizes is a common and well-accepted practice in simulation techniques, including many simulations of opioid use and overdose in US and other populations.[199] Thus, the present methodology is standard practice in my field, and this type of methodology, using available literature estimates to extrapolate to population sizes, is one that I have used in numerous studies that are published in peer-reviewed journals.[200–202] Using this methodology, Figure 13 provides my estimate of the prevalence of OUD in the US, West Virginia, and the Cabell Huntington Community from 2006 through 2018. Table 2 provides the numbers of OUD cases, multiplying the prevalence by estimates of population size. Cases in Cabell are estimated to range between 3,959 in 2006 to 8,252 in 2018. Using my methodology, I estimate the prevalence of OUD in the United States as ranging between 1.9% and 2.3% from 2006 to 2018. The prevalence in Cabell ranged from 4.2% to 8.8% over the same time period, which means that the prevalence of OUD in Cabell was between 1.7 and 4.9 times higher in Cabell than the US population from 2006 to 2018.

Figure 14 provides the distribution of my estimate of OUD cases in Cabell County stratified by the proportion that I estimate are directly attributable to prescription opioids (opioid use disorder due to prescription opioids), and indirectly attributable to prescription opioids (opioid use disorder due to heroin, multiplied by the minimum estimate of the proportion of heroin OUD cases that initiated opioid use with prescription opioids) using the minimum estimate of the initiation of opioid use with non-medical prescription opioids based on analysis of NSDUH data described in Section I. This approach provides a conservative estimate of the indirect attribution of heroin use to prescription opioids.

Figure 14. Number of individuals with opioid use disorder overall, directly attributable to prescription opioids, and indirectly attributable to prescription opioids, in the Cabell Huntington Community



H. Consequences of opioid use, disorder, and overdose for children in the Cabell Huntington Community

In order to estimate the burden of harm for the Cabell Huntington Community, I estimated harm directly within Cabell County; available evidence indicates that similar levels of harm are apparent in the City of Huntington. US Census estimates that the population size of Cabell County is 93,224 individuals as of 2018.[203] Approximately 19.7% of the population is under 18, thus there are approximately 18,365 children. Available evidence suggests that a significant number of children have, and will, experience substantial harm.

Given that I estimated that 8,252 adults in Cabell County experience mild to severe OUD, there are likely serious consequences of opioid use to children in Cabell County. While it is unknown what proportion of Cabell County opioid users are parents, planning for public health would suggest that administrators should be inclusive when estimating burden. Census data indicates that approximately 61% of Cabell County residents are between 18-64, a reasonable range for individuals parenting dependents 0-17 years old, thus, if 61% of the 8,252 adults are parents, then an upper bound estimate is that approximately 5,000 children in Cabell County are potentially exposed to parental opioid use during development.[204] In terms of consequences to developing fetuses and neonates, available data from Cabell County a substantial burden of NAS in Cabell County, as detailed in Table 1.

Available evidence indicates an extraordinary increase in both in the Cabell Huntington Community, and higher levels of overdose burden than nearly every other county in the country.[205] From 2000 to 2010, West Virginia as a whole had the second fastest growing prison population in the country, with an average annual change of an additional 133 individuals or 6.8% across the decade.[206] The prison population is expected to grow further as opioid use and use disorder continue to be a major burden on the justice system.[206] For the state of West Virginia as a whole, 34,000 children are estimated to have a parent in jail or prison, and an estimated 12.9% of prisoners have an opioid use disorder (which is likely an underestimate).[207] Further, an estimated 4,000 children in West Virginia have had a parent die from overdose or another opioid-related cause.[208] Available estimates indicate that 435 children were in the Cabell County foster care system as of May 2019,[209] which is an under-estimate of the number of children separated from parents and placed in other care situations; approximately 40% of foster care system placements are due to parental drug use, a substantial portion of which would be expected to be opioid use given the high burden of addiction in Cabell County. Overall, approximately 8.6 children per 1,000 in the state of West Virginia are separated from families due to concerns about child welfare, which is higher than any other state in the US.[210]

Children in the Cabell Huntington Community are expected to experience a large burden of psychiatric disorders and learning disorders throughout pre-school and school-age developmental periods due to in utero exposure to opioids as well as parental opioid use during development. Available estimates indicate that rates of psychiatric and learning disorders are approximately 2-3 times higher among children who experience parental drug use and parental separation or death, with ADHD, depression/anxiety, and PTSD among the leading disorders of children associated with parental drug use. The table below provides the US estimates[211] of any child mood disorder (including major depression, dysthymia, and bipolar), any anxiety disorder (including agoraphobia, generalized anxiety disorder, social phobia, specific phobia, panic disorder, post-traumatic stress disorder, and separation anxiety disorder), attention deficit hyperactivity disorder (ADHD), substance use disorder (including alcohol abuse/dependence and drug abuse/dependence), and any learning disability (based on a general population survey of parents querying whether a doctor, health professional, or school official ever told a parents that their child has a 'learning disability').[212] Given that the literature review conducted above indicates that in general, children who experience parental substance use have rates of disorders that are 2x to 3x times higher than other children, and that I estimate an upper bound for the number of children exposed to parental opioid use in Cabell County of 5,000, the table provides the estimated number of children in Cabell County who should be provided counseling, psychiatric and learning services during school age.

Approximate number of children in Cabell County in need of psychiatric and other services to manage symptoms			
	Prevalence in the general population[211]	Estimated prevalence among children exposed to parental drug use (2x to 3x higher risk)	Number of children in Cabell County potentially needing psychiatric or other services to manage symptoms due to parental opioid use
Any mood disorder	14.3%	28.6 to 42.9%	1,430 to 2,145
Any anxiety disorder	31.9%	63.8 to 95.7%	3,190 to 4,785
ADHD	8.7%	17.4 to 26.1%	870 to 1,305
Any substance use disorder	11.4%	22.8 to 34.2%	1,140 to 1,710
Learning disability	9.7%	19.4 to 29.1%	970 to 1,455

In summary, due to the high burden of opioid use, opioid use disorder, and the sequelae of these disorders for families and children, there is a high burden of need in the Cabell Huntington Community at each point in development. Pregnant women require evidence-based prenatal care including medication for opioid use disorder as needed; neonates require monitoring for congenital abnormalities, neonatal withdrawal, and growth and weight restriction; developing children need support for potential parental death, incarceration, abuse and neglect, as well as psychiatric disorders and learning problems as a result of parental substance use. I have discussed these analyses with local officials (including Tim Hardesty, Assistant Superintendent, Division of District Support and Employee Relations, Cabell County Schools, Kelly Watts, Assistant Superintendent, Division of Instruction and Leadership, Cabell County Schools, and Keith Thomas, Coordinator of Student Support, Cabell County Schools) who confirm experience in the community indicating that the burden of parental and caregiver opioid use to children in the Cabell Huntington Community is ongoing and significant, disrupting the home as well as the learning environment.

I. Prescription opioid use is causally related to heroin use

The available evidence establishes that prescription opioid use causally increases the risk for heroin use.[‡] Heroin and prescription opioids have similar pharmacological properties, thus there is the potential for substitution with one or the other when one is unavailable or available at lower cost.

The number of individuals who use heroin has been increasing in the United States.[213] Estimates of the number of individuals who use heroin in the United States were approximately 100,000 in the 1960s and 1970s, and heroin use was considered largely a problem of urban, low-income areas.[214] However, that has fundamentally changed in the US; as of 2010, available estimates were that there were 1.5 million individuals in the United States using heroin at least 4 times per month or more,[215] and there have been increases thereafter in heroin use as well. The demographics of heroin use are also changing, with increases in use across race, social class, gender, and urbanicity.[213,216] The increases in heroin use largely occurred among individuals who are or were prescription opioid users. Among individuals who use prescription opioids, heroin use increased by 138% from 2002-2004 to 2011-2013, and the connection is particularly strong among young adults.[217] Cross-sectional studies of samples recruited based on non-medical prescription opioid use and/or heroin use consistently find strong signals of a relationship. I reviewed 16 studies that found that individuals who use prescription opioids non-medically have higher rates of injecting and snorting heroin than individuals who do not use prescription opioids, even after controlling for health and mental health, as well as demographics.[216,218–232] While these studies are observational rather than experimental, in that no randomized clinical trial or experimental evidence has examined risk of heroin use following prescription opioid use, the studies are sufficiently diverse in population, valid in design and consistent in their results in order to draw the conclusion that prescription opioid use is causally related to heroin use.

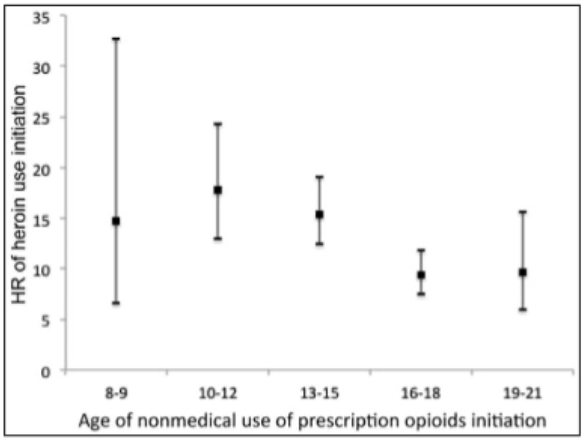
The available data consistently show that approximately 70-80% of individuals who used heroin in the last 20 years started their opioid use with prescription opioids. The most extensive report is from Cicero et al. (2014), reporting on data collected from 2,797 individuals seeking treatment for opioid use disorders.[216] Cicero et al. (2014) demonstrated that among those who initiated opioids in the 1960s through 1980s, less than one third used prescription opioids before heroin. From the 1990s on, as the supply of opioids increased, so too did the proportion of individuals who use heroin who began opioid use with prescription opioids (among those initiating in the 1990s, 50%; 2000s, 85%; 2010s, 78%). The figure that approximately 70-80% of individuals who use heroin begin with prescription opioids has been replicated in numerous other studies. Lankenau et al. (2012)[230] examined drug use histories among 50 individuals who inject drugs who had non-medically used opioids in the three months prior to the study, and documented that 86% of the sample used opioids non-medically prior to heroin use. Further, while individuals who use non-medically obtained

‡ It is not ethical or possible, of course, to conduct randomized controlled trials to demonstrate this effect. But where such studies are not possible, epidemiologists routinely rely on other kinds of evidence, including other types of studies such as those described in this Report.

opioids from a variety of sources including dealers, family, and friends, 75% of these individuals who use non-medically had obtained a prescription for opioids during their lifetime, and 2/5 of those reported that their own prescription was the initial source of opioid misuse. Pollini et al. (2011)[231] studied 123 individuals who inject heroin, documenting that 39.8% reported prescription opioid use prior to heroin use. Mateu-Gelabert et al. (2015)[232] interviewed 46 individuals who inject heroin, 70% of whom initiated opioid use with prescription opioids; mean age of first prescription opioid use was 17.9, and heroin use was 18.8 years; among individuals who use prescription opioids and heroin, the average difference in mean age of initiation between prescription opioids and heroin was 1.3 years. Ethnographers in New York, Philadelphia, San Francisco, Wilmington, and Ohio documented trajectories from medical and non-medical prescription opioid use to heroin, especially among younger cohort members.[219,220,224]

While studies of individuals who use heroin and other opioids interviewed about their drug use histories provide another signal, still more evidence from large-scale surveys and cohort studies has documented the relative risk of initiating heroin given prescription opioid use, compared to individuals who do not use prescription opioids. I cited above the evidence among adolescents and young adults that has found strikingly high estimated incidence rate ratios for the transition to heroin given non-medical prescription opioid use, even when controlling for individual-level risk factors that underlie a proclivity for drug use overall. There are also numerous studies that demonstrate strong relationships between non-medical prescription opioid use and heroin use among adults. Muhuri et al.[221] documented the association between prescription opioid use and heroin initiation estimated from age of onset reports across 9 years of the NSDUH. Pooled analyses indicated that the risk of heroin initiation was 19 times higher among those with prior non-medical prescription opioid use compared to those who did not use, even after controlling for a range of factors involved in the drug taking behavior. Banerjee et al. 2016[222] found that non-medical prescription opioid use was associated with more than 5 times increased hazard of heroin initiation compared to no use, even after adjusting for multiple risk factors. Data from Cerda et al., (2015)[223] are shown in Figure 15, and indicate that nonmedical prescription opioid use is associated with 10-15 times faster rate of transition to heroin use, across all ages of adolescence to young adulthood. Of those who reported new onset non-medical prescription opioid use, 27% subsequently initiated heroin. That prescription drug use is neither necessary nor sufficient to predict heroin use does not mean there is no causal relationship. In fact, the same can be said for many risk factors that are neither necessary nor sufficient to produce particular health outcomes, and yet have been shown to be causes of those outcomes. Examples include smoking and cancer; seat belts and deaths in automobile accidents; sedentary lifestyle and heart disease; and obesity and diabetes.

Figure 15. Fitted HRs of heroin initiation associated with prior nonmedical prescription opioid use, by age of nonmedical prescription opioid use initiation (NSDUH, 2004-2011)



Several additional points are worth keeping in mind. A small but significant proportion of individuals who use prescription opioids progress to heroin use.[221] However, heroin use does not need to be common in order to be causally related to prior use of prescription opioids. For example, all scientists would agree that smoking is a cause of lung cancer. In 2016 there were 218,229 new lung cancer cases in the United States (56 per 100,000 persons),[233] which makes lung cancer a rare disease. Yet smoking is no less a cause of lung cancer because lung cancer is rare than if it were common. By comparison, there were at minimum four times more heroin users (estimated 948,000 based on NSDUH data, which is likely an underestimate, thus at least a rate of 293.1 per 100,000)[234] in the United States than lung cancer cases; thus by comparison, heroin use is much more common. The existence of a causal relationship between risk factors and outcomes does not depend on prevalence. The number of individuals who use prescription opioids is approximately seven times larger than

the number of individuals who use heroin, thus while the absolute risk of transitioning to heroin given prescription opioid use is relatively small, the vast majority of individuals who use heroin began with prescription opioid use, and even small increases in progression to heroin use creates a significant public health burden.[217] Reasons cited for the transition to heroin use given prescription opioid use based on the research cited above are most often cost and convenience; prescription opioids are more expensive to obtain illegally than heroin, and more difficult in many geographic areas. Numerous factors predict transition from prescription opioid use to heroin use, including individual-level and community-level characteristics. However, the proportion initiating heroin increases in a dose-response relationship with the extent and length of prescription opioid use, providing further support for a causal relationship. Based on the evidence, it is reasonable to conclude that there is a causal relationship between prescription opioid use and heroin use, and that the increases in population-level heroin use in the United States are due, at least in significant part, to individuals who use prescription opioids transitioning to heroin use.

Another indicator that prescription opioid use is causally related to heroin use is the accumulating evidence that restricting prescription opioid supply among those who are dependent on opioids leads to an increase in heroin use and with risky patterns of use that cause opioid-associated death. A systematic review of 17 studies that evaluate the effectiveness of prescription drug monitoring programs indicated three of six studies found increase in heroin-associated death when supply is restricted through PDMPs, although noted that more research was needed given that methodological limitations precluded firm inference. Since then, additional studies with rigorous methodology confirm that, across different PDMP programs, as well as other restrictions on opioid supply, such as OxyContin reformulation, an increase in heroin overdose is a consequence of some supply restrictions, due to the restriction of prescription opioids among individuals who are dependent on them. For example, Martins et al. (2019) found that states with certain PDMP features had increases in heroin overdose by 19%.[105] Importantly, not all PDMP programs were associated with an increase in heroin overdose death, indicating that transition is not inevitable if additional supports are in place for drug users. Additionally, Alpert et al. (2018) analyzed variation in OxyContin misuse across states to demonstrate that those states with the highest OxyContin misuse prior to reformulation had the highest increases in heroin overdose after the reformulation.[235] This evidence certainly points to a mechanism in which individuals who are dependent on prescription opioids transition to heroin after supply or potency is curtailed. Of note, a connection between reductions in opioid prescribing and increases in heroin overdose should not be interpreted as a signal that opioid supply policies are misguided; rather, they are indicative that: 1) the reduction in opioid supply is not sufficient to curtail the extensive harm associated with the initial public health burden of widespread opioid oversupply; 2) there is a causal connection between opioid products (prescription opioids to subsequent heroin use); and 3) the need for a robust and integrated system of treatment and services for those affected has never been more urgent.

Finally, since approximately 2013, overdose deaths due to synthetic opioids (e.g., fentanyl) have been exponentially increasing in the United States. These synthetic opioids are much more potent than heroin; less than 2 mg of fentanyl, equivalent to approximately two grains of salt, can cause overdose.[236] Available evidence indicates that fentanyl and other highly-potency opioids have been adulterating the supply of both heroin and illicitly manufactured prescription opioids.[237] Given the evidence that prescription opioid use is causally related to heroin use, prescription opioid use is also responsible for the increase in fentanyl and other synthetic opioid harms. Indeed, individuals who use prescription opioids who both obtain illicitly manufactured prescription opioids, as well as heroin, will be potentially exposed to fentanyl, increasing the risk of overdose and death. In terms of the magnitude and scope of the relationship, given that available estimates indicate that approximately 70-80% of individuals who use heroin began their opioid-using trajectories with prescription opioids, I estimate that approximately 70-80% of fentanyl-involved opioid deaths are attributable to prescription opioid use.

Quantifying the proportion of opioid use that is attributable to prescription opioids. Given that approximately 70-80% of individuals who use illicit opioids will first use prescription opioids before starting other opioids such as heroin, and that the preponderance of evidence support the conclusion that prescription opioid use is causally associated with heroin and other opioid use, it is reasonable to conclude that a substantial proportion of

heroin and other opioid deaths in the United States, and in the Cabell Huntington Community, are attributable to prescription opioid use. That is, prescription opioid distribution and the first wave of the opioid epidemic set the stage for all that has followed, and the evidence indicates that had the prescription opioid epidemic not occurred, there would be no heroin and high-potency synthetic overdose crisis. I designate between deaths that are directly attributable to prescription opioids, which include those for which prescription opioids were listed as a contributing factor on the death certificate. Deaths indirectly attributable to prescription opioids include opioid deaths for which prescription opioids were not listed on the death certificate, but that we can conservatively estimate can be attributed to the initiation of opioid use with prescription opioids.

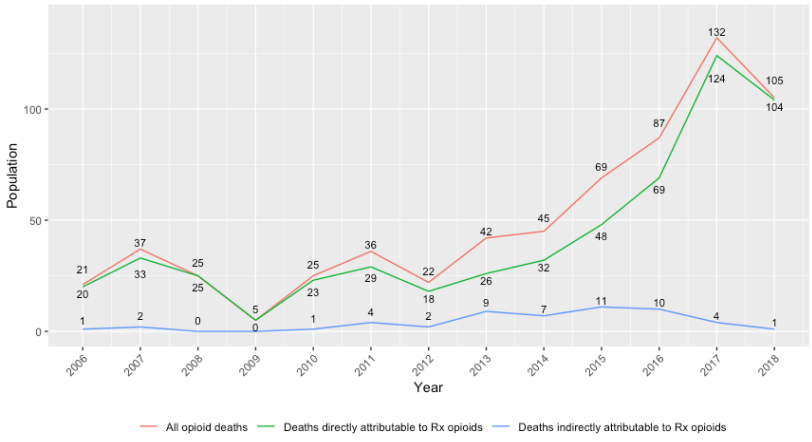
Indeed, using the estimates that I derived from existing studies to estimate the total proportion of regular and dependent opioid users in the Cabell Huntington Community, I can provide a conservative estimate of the extent to which these cases are directly attributable to prescription opioids (prescription opioid listed as a contributing factor) as well as indirectly attributable to prescription opioids (prescription opioids not listed as a contributing factor to the death, but the death remains attributable based on the estimate that opioid use most often begins with prescription opioids). The causal attribution of these cases to an initial set of causes and conditions follows the epidemiological standard of component causes theories, articulated by both Rothman and others in well-accepted epidemiological textbooks,[238] including my own.[14,239] A factor is a component cause if it is a necessary but insufficient cause of at least some cases of the outcome, in this case regular or dependent use of opioids. That is, among those who are currently using a non-prescription opioid such as heroin, prescription opioids are a component cause if among some of those individuals, the heroin use would not have occurred without the initial use of prescription opioids.

First, the proportion of individuals with opioid use disorder that are directly attributable to prescription opioids in each year can be estimated by applying the annual ratio of prescription opioid use disorder to total opioid use disorder based on NSDUH data. Specifically, this ratio is calculated using rates of prescription opioid use disorder and heroin use disorder for West Virginia (NSDUH restricted-use data analysis system [RDAS]), the 10.4% overlap of heroin use disorder and prescription opioid use disorder (NSDUH RDAS), and the population of Cabell County (CDC Wonder). Second, for those cases that are not directly attributable to prescription opioids, I estimate that a substantial proportion remain attributable to prescription opioids. Indeed, available literature reliably indicates that 70-80% of individuals who use heroin and other opioids also used prescription opioids prior to the start of heroin and other opioid use. In providing an estimate for the proportion of OUD and opioid deaths indirectly attributable to prescription opioids, I selected the most conservative approach that would provide the lower bound of the proportion that can be attributed to prescription opioids. To do so, I used the percentage of respondents reporting lifetime heroin use who first used prescription drugs before or at the same age as first use of heroin, and averaged this across NSDUH years with available data (2008-2014). The coding follows that of the Cerda et al. 2015 paper, "Nonmedical Prescription Opioid Use in Childhood and Early Adolescence Predicts Transitions to Heroin Use in Young Adulthood: A National Study."[223] However, this methodology provides a conservative estimates compared to the existing literature, for several reasons. First, as discussed throughout this report, the NSDUH is primarily a household sample and does not include individuals who are incarcerated or in other institutional settings, and under-represents heroin and other drug users. Indeed, as noted in other sections of this report, the estimate of individuals with OUD is substantially under-estimated in the NSDUH data, and as such, the reports of non-medical prescription opioid use are likely under-reports as well. Second, the NSDUH data that I analyzed asked survey respondents specifically about their history of non-medical prescription opioid use, thus under-counting initiation with prescription opioids obtained in a medical setting. Thus, estimating the proportion of non-medical prescription opioid use that preceded heroin use among NSDUH respondents provides the most conservative, or minimum-bound, approach to estimating the proportion of OUD cases and deaths for which prescription opioids were not listed as a contributing factor that are indirectly attributable to prescription opioids in the West Virginia and the Cabell Huntington Community. Using this methodology, I estimated the proportion of heroin users who report non-medical prescription opioid use at an age equal to or prior to the age in which they began using heroin. Across years, this prevalence estimate ranged from 45.5 in 2006 to 62.8 in 2014. Averaging across those years, a minimum

of 53.4% of opioid use disorder cases and deaths in the Cabell Huntington Community are indirectly attributable to prescription opioids, averaged across years from 2006 to 2014. Figure 13 provides the number of individuals with opioid use disorder that I estimate to due directly to prescription opioids, indirectly due to prescription opioids, and the total attributable to prescription opioids. The average of 53.4% is lower than the broader literature estimate that 70-80% of individuals who use heroin and other illicit opioids begin with prescription opioids; this is expected, given the undercounting of these cases in the NSUDH data, thus the two estimates are quite comparable – at minimum, more than half of heroin OUD cases and deaths are attributable to prescription opioids, and the broader literature supports that had all heroin and other illicit opioid cases been sampled, the true proportion is close to three quarters.

Using the same methodology outlined above, I can estimate the minimum of the total number of deaths from opioid overdose in Cabell County that are directly and indirectly due to prescription opioids, as well as deaths due to non-prescription opioids. Opioid overdose deaths for which a prescription opioid was listed on the death certificate as a contributing cause are deemed directly due to prescription opioids. Among other deaths, I estimate that a minimum of 53.4% of deaths are indirectly due to prescription opioids, given the NSDUH data estimates of the proportion of non-prescription opioid use disorder for which prescription opioids were a preceding substance use. Therefore, Figure 16 provides the total number of opioid overdose deaths in Cabell County for each year from 2006 through 2018, with the number directly attributable and minimum number indirectly attributable to prescription opioids.

Figure 16. Number of deaths attributable to opioids overall, directly attributable to prescription opioids, and indirectly attributable to prescription opioids, in the Cabell Huntington Community



J. The impact of diverted opioids was not random, but part of a complex system that involved community level economic conditions

The exponential increases in the opioid supply, and the resulting opioid diversion and related harms, did not occur in isolation. It is important to put in context that opioid use disorder and overdose disproportionately affected economically deprived areas, and also interacted with individual-level risk factors for use. However, ready access to prescription opioids was a necessary precondition to their widespread availability and uptake.

The relationship between shifting macroeconomic conditions and drug poisonings has received considerable attention since the publication of Case and Deaton's widely-discussed paper.[240] In their 2015 paper, Case and Deaton reported a recent spike in mortality rates among less-educated non-Hispanic Whites, and posited that long-term shifts in the labor market, reduced employment opportunities, and overall life prospects for persons with a high school degree or less, have driven increases in "deaths of despair" (i.e., deaths from suicides, cirrhosis of the liver, and drug poisonings). This model suggests that the increased rates of opioid-related mortality over the past three decades are attributed to shifting macroeconomic conditions. However, several studies contradict the narrative that the rise of deaths in the United States is due to a common source such as "despair". In a working paper by Ruhm (2018),[241] known measures of economic factors predicted drug and opioid overdose, but explained very little of the variation in rates over time. Further, Masters et al. (2018)[242] reanalyzed vital statistics data by gender, age, and birth cohort, and concluded that drug overdose rates increased across a wide range of age groups, especially those in young and middle adulthood, and did not mirror trends for other "despair"-related death such as suicide, indicating that the drivers of opioid-related deaths in the United States were factors that could influence a broad range of age groups simultaneously. Indeed, the evidence that prescription opioids have an independent effect on risk of

death, and that availability was the principal driver of prescription opioid use rather than economic conditions, is supportive of the role of availability rather than economic factors as the principal causal factor in driving increases in opioid-related harm.

While there is considerable literature on macroeconomic conditions and opioid-related mortality, four studies form the highest rigor of the evidence base.[241,243–245] One of these studies[243] found that average drug-related mortality rates were higher in counties with greater economic and family distress and in counties with greater population share dependent on mining, compared to other areas of the labor market, and lower in counties with more religious establishments, higher percentage of recent in-migrants, and counties with greater population share dependent on public sector employment; two other studies[240,244] found that a 1% increase in county unemployment rate was associated with a 0.19 per 100,000 increase in opioid-related mortality rate (3.6%) and that the estimated change in mortality accounted for by worsening economic conditions ranged from 5 to 7% for Prescription Opioid-related mortality and 2 to 5% for illicit opioid-related deaths at the 3-digit ZIP code level, indicating that economic conditions account for less than one-tenth of the rise in mortality rates over time. Finally, Pear et al.[245] found that two area-level indicators, percent in poverty and percent of adults with less than a high school education, were associated with higher rates of prescription opioid related mortality, while median household income was associated with lower rates. However, urbanicity modified the association between macroeconomic conditions and rates of heroin-related mortality, with poverty and unemployment associated with increases in heroin-related mortality in metropolitan areas and low educational attainment alone associated with heroin-related mortality in rural areas. Limitations of the extant research are that publicly released files do not include all deaths (to reduce the potential for confidentiality violations),[243] inadequate measure of outcome,[243] failure to account for area-level prescription opioid supply,[243,245] and no investigation of the stability of effect estimates at different levels of organization.[241,243–245]

In summary, there is evidence that the population distributions of prescription opioid and other opioid mortality disproportionately affected economically deprived areas; however, the available evidence indicates that economic conditions played a relatively small part in increased opioid-related morbidity and mortality. The driving force in increasing opioid-related morbidity and mortality was access to and wide-spread availability of opioids.[§]

K. Availability principles and the relationship with harms related to prescription opioids

Arguments have been made that the increases in prescription opioid overdose and addiction in the United States are largely driven by individuals who use non-medically, and that as prescription opioids have become more difficult to obtain because of changes to the changes to prescription opioid supply (e.g., prescription drug monitoring programs, physician education), those who use drugs have progressed to heroin and other more available and less expensive opioids to satiate addiction. While certainly there is data that rates of overdose, addiction, and harm among those who use opioids non-medically are high, there is evidence that harm among those who use opioids medically is also high. Further, as the data cited in this report show, the proportion of individuals with opioid use disorder that receive a prescription at some point from a physician is more than half, and the risk of addiction given medical use of opioids at high doses for long periods of time is many times higher for high dose than low dose prescriptions (e.g. Edlund et al.[60] estimate that rates of opioid use disorder among those prescribed high doses is 50 times that of those who receive low doses). Rates of opioid distribution and opioid related death vary substantially across geographic areas, and all available evidence indicates that prescription opioids harms, due to medical use as well as diversion, increase with the supply of opioids. With regard to recent decreases in the opioid supply, there is evidence that restricting the prescription opioid supply is associated with greater transition to heroin,[97] and that this transition has influenced death rates due to the contamination of heroin with fentanyl and other synthetic opioids. As such, abatement that is broad ranging in scope is necessary. However, the notion that the current

[§] It is beyond the scope of this report to review or discuss the impact of economic conditions on treatment and abatement needs, which may be important to consider in the remedial context.

opioid epidemic is due to economic conditions or despair/depression is not supported by data. There is no evidence that depression has increased across time among adults in the US, and available evidence from economic studies of the role of economy in drug overdose have suggested that there is a limited role for economic conditions; based on the studies and data discussed above, the role of opioid supply is so much more strongly correlated that no reasonable interpretation of the data would support the conclusion that economic conditions are greater than supply in producing the observed trends. The validity of the principle that addiction increases as availability increases has been established in multiple contexts, and it is highly probable that increased availability of prescription opioids is the driving force contributing to OUD, overdose morbidity and mortality, and NAS

Indeed, there are decades of public health research that have a strong analogy to the current opioid epidemic. The relationship between supply of an addictive substance and subsequent rates of substance use disorder has been well established in the public health literature for years through principles of availability.[246] Succinctly, this principle posits that one driver of population burden related to substance use harm is the availability and cost of the substance.[247,248] The relationship between availability/cost and harm has been extensively documented for decades for alcohol and tobacco, and it is one reason that alcohol and cigarette taxes, minimum pricing, and other public health efforts aimed at availability and price are among the most effective population-level interventions to reduce alcohol-related harms, such as alcohol-impaired driving fatalities.[249–251] In summary, as prescription opioids became more commonly available in the market, decades of prior work across numerous substances would predict a rise in opioid-related harm, and in fact, supportive evidence has been shown across numerous substances and time periods and populations.

L. Comparison of deaths due to prescription opioids with NSAIDs

Among the threads of inquiry related to the increases in opioid-related harm in the United States are comparisons to harm associated with other pharmaceutical products that also cause harm in some users. For comparison, non-steroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed for a range of conditions, including pain, but also arthritis and other inflammatory conditions, as well as fever. Common forms of NSAIDs are available over-the-counter, such as aspirin and ibuprofen, but a range of products are available by prescription as well. NSAIDs are prevalent, and their use varies across age. Data from the National Health and Nutrition Examination Surveys from 1999-2004 indicated a past-year prevalence of 26.1% of the US population for all NSAID use, and 9.5% for prescription NSAID use.[252] While use is common, it comes with health risks, including, for example, cardiovascular events. Available reviews and meta-analysis suggests that the risk of serious GI events with extended NSAID treatment is between 1-3%, which is approximately 10 times higher than the background rate in the population.[253–257]

Given their potential for harm and that both are used to treat pain, it is worth comparing the deaths due to NSAIDs with the deaths due to prescription opioids. It has been estimated that 16,500 per year are due to GI bleeding from NSAID use. This estimate, however is not reliable. It is based on a single article that extrapolated from 19 deaths among 4,258 patients in an administrative database,[258] multiplying the 19 deaths by estimated population size. Such extrapolation is not quantitatively specific due to measurement error in death rates, and further, the cohort from which the 19 deaths were observed was among a sample with rheumatoid arthritis, among whom the baseline mortality rates are higher than the general population. Another study estimated deaths due to NSAIDs to be closer to 3,200 deaths,[259] but this too is not a reliable estimate. The estimate of 3,200 deaths is based on the estimate of the attributable fraction for NSAID and death. The attributable fraction (an estimate of the proportion of deaths that are causally related to an exposure) varies based on the baseline prevalence of exposure. Thus, the authors multiplied the attributable fraction in the study sample by the proportion of the US population that used any NSAID in the previous week (regardless of dose or duration), based on a phone survey of 2,590 individuals, which is not a large sample size for total population extrapolation. Further, applying a summary attributable fraction is incomplete, as it does not take into consideration type and dose (e.g., any NSAID use counts at the same level of risk as long-term use); it is well known that the prevalence of NSAID use varies widely by race, sex, and age,[252] such that applying one average to the whole population without incorporating subgroup heterogeneity will include substantial error.

Solomon et al. (2010)[260] directly compared the risks associated with NSAID to those with prescription opioids as well as cyclooxygenase 2 inhibitors (coxibs) among a large claims database of low-income older adults who were Medicare beneficiaries in Pennsylvania and New Jersey and had diagnoses of osteoarthritis or rheumatoid arthritis on 2 separate visits (N=36,414). Authors used a propensity score to balance potential confounding factors among those using NSAIDs, coxibs, and opioids. The use of a propensity score in this analysis is important and rigorous, as it controls for the potential reasons why an individual would be prescribed, for example, NSAIDs over opioids. Once matched on propensity scores, the three groups were balanced on over 40 covariates including demographics, clinical characteristics, health history, and use of other medications. Further, the authors included incident use of medications in the comparison groups, which further helps to establish causality, and examined incident health events. Comparing prescribed NSAIDS to prescribed opioids, those prescribed opioids had higher rates of a range of adverse events including cardiovascular events, fractures, kidney injury and falls, and approximately equivalent rates of events such as GI bleeding. And finally, the mortality rate among opioid users was 75 per 1000 patient years among prescribed opioid users, compared to 47 per 1000 patient years among prescription NSAID users over the course of the study, for an increased hazard of death of 1.87 times that of NSAID users. While the particular hazard ratios may differ in other populations, there is no *a priori* reason to doubt the applicability of Solomon *et al.'s* general conclusion that prescription opioids are associated with greater incidence of adverse events and mortality. With that in mind, however, Solomon et al. (2010) remains the most rigorous study to date that has directly compared the harm of medical prescription opioid use with medical NSAID use, and determined that mortality as well as a wide range of medical morbidities was higher, substantially so, for opioids compared with NSAIDs.

Exhibits to this Report:
Attached as Exhibit A is a copy of my current curriculum vitae and a list of all publications authored by me in the past 10 years.
Attached as Exhibit B is a list of data or other information considered by me in forming the opinions expressed herein.
Attached as Exhibit C is a statement of my compensation for services performed in this case.
Attached as Exhibit D is a list of all cases in which I have testified as an expert at trial or by deposition during the past four years.

Pursuant to 28 U.S.C. Section 1746, I declare under penalty of perjury that the foregoing is true and correct.

Executed on: August 3, 2020

Katherine Keyes

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long-term exposure: a systematic review. *Med J Aust*. 2006;185(9):501-506. doi:10.5694/j.1326-5377.2006.tb00665.x

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257. Richy F, Bruyere O, Ethgen O, et al. Time dependent risk of gastrointestinal complications induced by non-steroidal anti-inflammatory drug use: a consensus statement using a meta-analytic approach. *Ann Rheum Dis*. 2004;63(7):759-766. doi:10.1136/ard.2003.015925
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259. Tarone RE, Blot WJ, McLaughlin JK. Nonselective nonaspirin nonsteroidal anti-inflammatory drugs and gastrointestinal bleeding: relative and absolute risk estimates from recent epidemiologic studies. *Am J Ther*. 2004;11(1):17-25.
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Katherine Keyes, PhD Expert Report

Case No. 1:17-op-45053-DAP and No. 1:17-op-45054 Opioid Litigation

EXHIBIT A

Curriculum Vitae

Katherine M. Keyes, PhD
Department of Epidemiology
Columbia University
722 West 168th Street
New York, NY 10032
(212) 305-6706
kmk2104@columbia.edu

Date of Preparation: July 8, 2020

Personal Data:
Name: Katherine Keyes
Birthplace: Minneapolis, MN
Citizenship: USA

Academic Appointments/Work Experience

7/1/2016 – Present	**Department of Epidemiology** **Mailman School of Public Health, Columbia University** *Associate Professor of Epidemiology*	New York, NY
2/1/2012 – 6/30/2016	**Department of Epidemiology** **Mailman School of Public Health, Columbia University** *Assistant Professor of Epidemiology*	New York, NY
11/15/2010-1/31/2012	**Mailman School of Public Health, Columbia University** *Instructor in Epidemiology*	New York, NY
7/1/2013 – 6/30/2016	**Department of Psychiatry** **Mailman School of Public Health, Columbia University** *Assistant Professor of Epidemiology (in Psychiatry)*	New York, NY
1/2015 – Present	**Survey Research Center, Institute for Social Research** **University of Michigan** *Adjunct Research Assistant Professor*	Ann Arbor, MI

7/2018 – Present	**Society and Health Research Center** **Universidad Mayor** *Adjunct Associate Professor*	Santiago, Chile

Education

09/2006 – 06/2010	**Columbia University**, **Mailman School of Public Health** PhD: Epidemiology, June 2010 Thesis title: *Ecologic-level disapproval and the prevalence of substance use: A multi-level age-period-cohort analysis of high-school attending adolescents in the United States* Sponsor: Deborah Hasin	New York, NY
09/2004 – 05/2006	**Columbia University**, **Mailman School of Public Health** MPH: Epidemiology, May 2006	New York, NY
09/1998 – 12/2001	**University of Minnesota** BS: Finance, BA: Theater Arts, December 2001	Minneapolis, MN

Training

06/2010 – 01/2012	**Columbia University** *Epidemiology Merit Post-Doctoral Fellow*	New York, NY
09/2006 – 06/2010	**Columbia University** *Psychiatric Epidemiology Pre-Doctoral Training Fellow (T32 MH013043, PI: Link)*	New York, NY

Honors and Awards

Carol Hogue Mid Career Award, Society for Epidemiologic Research, 2020
NIH Early-Stage Investigator, Office of Disease Prevention, 2017
Robins-Guze early career investigator award, American Psychopathological Association, 2016
Michelle Tansella Award, World Psychiatric Association Epidemiology section, 2016
Calerdone Junior Faculty Prize, Mailman School of Public Health, Columbia University, 2016
Tow Scholarship, Mailman School of Public Health, Columbia University, 2015
Research Society on Alcoholism Young Investigator Award, 2015
Columbia Psychiatric-Neurological Epidemiology Early Investigator Award, 2012
Robert Wood Johnson Health and Society Scholars Fellowship, 2010 (declined)
William Farr Award in Epidemiology, Columbia University, 2010
Student Merit Travel Award, Research Society on Alcoholism, 2009
Student award, Epidemiology Section, American Public Health Association, 2009
First place, Division 50 Student Poster Competition, American Psychological Association, 2009

National Institute of Drug Abuse Travel Award, American Psychological Association, 2009
Student Merit Travel Award, Research Society on Alcoholism, 2008
Gordis Award for outstanding student research, Research Society on Alcoholism, 2008
Lilienfeld Prize for Student Research, Society for Epidemiologic Research, 2008
Student Merit Travel Award, Research Society on Alcoholism, 2007
Finalist, Gordis Award for outstanding student research, Research Society on Alcoholism, 2007
Women & Gender Junior Investigator Award, College on Problems of Drug Dependence, 2006
Student Merit Travel Award, Research Society on Alcoholism, 2006

Administrative Leadership and Academic Service

ACADEMIC SERVICE

- Methods qualifying exam committee, 2015-present

ADMINISTRATIVE LEADERSHIP AT CUMC AND NYP

- Irving Institute for Clinical and Translational Research, KL2 career and training award reviewer, 2017-2019

Professional Organization and Societies

MEMBERSHIPS AND POSITIONS

American Psychopathological Association (2006-present)
- Nominations committee, 2013
- Robins-Guze early career investigator award recipient, 2017

Research Society on Alcoholism (2006-present)
- Program committee, 2015-present
- Young Investigator Award recipient, 2015

Society for Epidemiologic Research (2007-present)
- Lilienfeld award recipient, 2008
- Education committee member, 2015-2018
- Education committee chair, 2019-present
- Member-at-Large, Executive committee, 2018-present
- Carol Hogue Mid Career Award, 2020

Society for Research on Child Development (2012-present)
- Thornberg Dissertation Award committee, 2014-2018
- Communications committee, 2017-2019

World Psychiatric Association Epidemiology and Public Health Section (2011-present)
- Michelle Tansella Award recipient, 2016
- Executive committee, 2016-present
- Local host of 2018 meeting, held at Columbia University, New York, May 2-4th, 2018

NIH STUDY SECTIONS
• NIAAA: AA1: Biomedical Research Review Subcommittee, November 9th, 2015
• NIAAA: AA1: Biomedical Research Review Subcommittee, July 11th, 2016
• NIDA: Special Emphasis Panel: PAR-16-24: Accelerating the Pace of Drug Abuse Research Using Existing Data, November 4th, 2016
• NIAAA: AA2: Epidemiology, Prevention and Behavior Research Review Subcommittee, March 6th, 2017
• Social Sciences and Population Studies-B (SSPB) study section, June 15th, 2017
• NIAAA: AA1: Biomedical Research Review Subcommittee, July 14th, 2017
• NIAAA: AA2: Epidemiology, Prevention and Behavior Research Review Subcommittee, March 5th, 2018
• NIDA: Special Emphasis Panel: PAR-16-24: Accelerating the Pace of Drug Abuse Research Using Existing Data, March 1st, 2018
• CSR Special Emphasis Panel: Tobacco Control Policies to Reduce Health Disparities, March 29, 2019.
• NIAAA: AA2: Epidemiology, Prevention and Behavior Research Review Subcommittee, Standing member. 2019-present

NATIONAL COMMITTEE MEMERSHIP
National Academy of Sciences, Engineering, and Medicine: Health and Medicine Division
"Accelerating the Progress to Reduce Alcohol-Impaired Driving Fatalities"
2017-2018

JOURNAL REVIEWER
Addiction; Alcoholism: Clinical and Experimental Research; American Journal of Epidemiology; American Journal of Psychiatry; American Journal of Public Health; Archives of General Psychiatry; BMC Psychiatry; British Journal of Psychiatry; Contemporary Drug Problems; Demography; Depression and Anxiety; Drug and Alcohol Dependence; Epidemiology; International Gambling Studies; International Journal of Epidemiology; JAMA; JAMA Pediatrics; JAMA Psychiatry; Journal of Nervous and Mental Diseases; Journal of Psychiatric Research; Journal of Traumatic Stress; Journal of Studies on Alcohol and Drugs; Molecular Psychiatry; New England Journal of Medicine; Preventive Medicine; PLoS One; Psychological Medicine; Social Psychiatry and Psychiatric Epidemiology; Social Science and Medicine; Substance Abuse Treatment, Prevention, and Policy

ABSTRACT REVIEW
Society for Epidemiologic Research

EDITORIAL BOARD

CURRENT
• Drug and Alcohol Dependence, Associate Editor, 2015 to present
• American Journal of Public Health, guest editor, Special Issue: "Improving Population Mental Health in the 21st Century", 2019

• Alcoholism: Clinical and Experimental Research, Field Editor, 2014 to present
• Injury Epidemiology, Associate Editor, 2013 to present

FORMER
• BMC Psychiatry, Associate Editor, 2011 to 2015
• Social Psychiatry and Psychiatric Epidemiology, Editor of commentaries and editorials, 2014 to 2016

CONSULTING

Expert witness, National Prescription Opioid Litigation, Northern District of Ohio (MDL 2804)
Expert witness, New York State opioid litigation, on behalf of the People of the State of New York

Fellowship and Grant Support

ACTIVE RESEARCH FUNDING

"Suicide as a contagion: modeling and forecasting emergent outbreaks" (PIs: Keyes and Shaman)
R01 MH 121410
Role on project: Co-principal Investigator and contact PI (multiple PI with Jeff Shaman)
Dates of funding: 01/24/2020-11/30/2024
Funder: National Institute of Mental Health
Total direct and indirect costs: $665,349.00

"As adolescent substance use declines, internalizing symptoms increase: identifying high-risk substance using groups and the role of social media, parental supervision, and unsupervised time" (PI: Keyes)
R01-DA048853
Role on project: Principal investigator
Dates of funding: 07/01/2019-06/30/2024
Funder: National Institute of Drug
Total direct and indirect costs: $434,794

"Age, period, and cohort effects on gender differences in alcohol use and alcohol-related problems in 47 national, longitudinally-followed cohorts" (PIs: Keyes and Jager)
R01-AA026861
Role on project: Co-principal investigator and contact PI (Multiple PI with Justin Jager)
Dates of funding: 07/01/2018-06/30/2023
Funder: National Institute of Alcohol Abuse and Alcoholism
Total direct and indirect costs: $529,899

"Diverging trends between depression/suicidality and alcohol/opioid use among adolescents in the United States: Subgroup variation and the role of social media in 2 samples of adolescents" (PI: Keyes)
R49 CE002096, subproject of CDC injury center resubmission
Role on project: Principal investigator
Dates of funding: 07/01/2019-06/30/2021
Funder: Centers for Disease Control and Prevention
Total direct and indirect costs: $200,000

"CHASE: an innovative county-level public health response to the opioid epidemic in New York State" (PIs: El-Bassel, Feaster, Gilbert, Nunes)
UM1 DA049415
Role on project: Co-Investigator
Dates of funding: 04/17/2019-03/31/2023
Funder: National institute on Drug Abuse
Total annual direct and indirect costs: $22,510,844

"Columbia Injury Control Research Center" (PI: Branas)
R49 CE002096
Role on project: Research Director
Dates of funding: 08/01/2019-07/31/2020
Funder: Centers for Disease Control and Prevention

"Is social media affecting adolescent mental health? Piloting machine learning techniques to identify at-risk youth in national samples of adolescents from 2009 through 2018."
Role on the project: Principal Investigator
Funder: Columbia Population Research Center
Dates: May 2019-May 2020
Total direct costs: $15,000

"Impact of medical and recreational marijuana laws on cannabis, opioids, and psychiatric medications: national study of VA patients, 2000-2024" (PI: Hasin)
Role on project: Co-Investigator
Dates of funding: July 2019 – April 2024
Funder: National Institute on Drug Abuse (R01-DA048860)
Total direct and indirect costs: $611,811

"Examining the synergistic effects of cannabis and prescription opioid policies on chronic pain, opioid prescribing, and opioid overdose" (PI: Martins and Cerda)
Role on project: Co-Investigator
Dates of funding: January 2019 – November 2023
Funder: National Institute on Drug Abuse (R01-DA045872)
Total direct and indirect costs: $730,223

"Drug use among nightclub and dance festival attendees in New York City" (PI: Palamar)
Role on project: Co-Investigator, PI of Columbia subcontract
Dates of funding: 09/01/2018-05/31/2021
Funder: National Institute on Drug Abuse (R01-DA044207)
Total direct and indirect costs: $497,339

"Monitoring the Future: Drug Use and Lifestyles of American Youth" (PI: Miech)
Role on project: Co-Investigator, PI of Columbia subcontract
Dates of funding: August 2017 – June 2022
Funder: National Institute on Drug Abuse (R01 DA001411)
Direct costs: $5,123,733

PAST SUPPORT

"Substance abuse history, mental health and firearm violence: from evidence to action" (PI: Keyes and Cerda)
Role on project: Principal investigator and Contact PI (Multiple PI with Magdalena Cerda)
Dates of funding: June 2015 – May 2019
Funder: National Institute of Alcohol Abuse and Alcoholism (R21 DA041154)
Direct costs: $275,000

"Race, alcohol consumption, and vehicle crashes: an epidemiologic paradox" (PI: Keyes)
Role on project: Principal investigator
Dates of funding: June 2013 – May 2019
Funder: National Institute of Alcohol Abuse and Alcoholism (K01AA021511)
Direct costs: $849,849

"Aging well with alcohol? Harnessing longitudinal data from 20 countries to understand health impacts of moderate drinking among older adults" (PI: Keyes)
Role on project: Principal investigator
Dates of funding: June 2017 – May 2019
Funder: The Robert N. Butler Columbia Aging Center
Direct costs: $30,000

"State medical marijuana laws and NSDUH marijuana use and consequences since 2004" (PI: Martins)
Role on project: Co-Investigator
Dates of funding: August 2013 – December 2018
Funder: National Institute on Drug Abuse (R01 DA037866)
Direct costs: $ 750,000

"State medical marijuana laws and teen marijuana use and attitudes since 1991" (PI: Hasin)

Role on project: Co-Investigator, PI of Columbia subcontract
Dates of funding: August 2012 – July 2017
Funder: National Institute on Drug Abuse (R01 DA034244)
Direct costs: $ 374,562

"Neighborhood interventions in alcohol-related homicide: a systems approach" (MPI: Keyes and Cerda)
Role on project: Principal investigator and Contact PI (Multiple PI with Magdalena Cerda)
Dates of funding: October 2013-September 2016
Funder: National Institute of Alcohol Abuse and Alcoholism (R21 AA021909)
Direct costs: $275,000

"Racial/Ethnic Disparity in Alcohol-Attributable Mortality from Motor Vehicle Crashes"
Role on project: Principal investigator (PI)
Dates of funding: January 2016 – December 2016
Funder: Columbia University Center for Injury Epidemiology and Prevention
Direct costs: $10,000

"Correcting nonresponse bias in national surveys"
Role on project: Principal investigator
Dates of funding: November 2015-October 2016
Funder: Columbia University Calderone Junior Faculty Prize
Direct costs: $25,000

"Principles of Epidemiology: a flipped classroom proposal"
Role on the project: Principal Investigator (Multiple PI with Silvia Martins)
Dates of funding: May 2015 to May 2016
Funder: Columbia University Provost Hybrid Learning Course Redesign and Delivery program
Direct costs: $12,000

"Mental health and firearm violence: from evidence to action (MPI: Keyes and Cerda)
Role on project: Principal investigator (Multiple PI with Magdalena Cerda)
Dates of funding: January 2015 – December 2015
Funder: Columbia University Center for Injury Epidemiology and Prevention
Direct costs: $10,000

"Developing a translational framework for studying grief and grief-related pathologies"
Role on the project: Co-Investigator (PI: Zoe Donaldson)
Dates of funding: May 2015 – September 2015
Funder: Columbia University Collaborative and Multidisciplinary Pilot Research Awards

Direct costs: $15,000

"Does structural discrimination explain health disparities by race? Preliminary analyses in state-to-state mobility" (PI: Keyes)
Role on project: Principal investigator
Dates of funding: December 2012 – June 2013
Funder: Robert Wood Johnson Health & Society Scholars Program at Columbia University
Direct costs: $5,000.00

Research Associate Award: "The longitudinal emergence of racial/ethnic differences in alcohol use disorders and depression from adolescence to adulthood" (PI: Keyes)
Role on project: Principal Investigator
Dates of funding: September 2011 – June 2012
Funder: Columbia University
Direct costs: $30,000.00.

"Period and cohort effects in adolescent substance use: testing the effects of the social environment in a time series of U.S. adolescents from 1976-2008" (PI: Keyes)
Role on project: Principal Investigator
Dates of funding: December 2010 – June 2011
Funder: Robert Wood Johnson Health & Society Scholars Program at Columbia University
Direct costs: $10,000.00

"Age-period-cohort effects on substance use in adolescence, 1976-2006" (PI: Keyes)
Role on project: Principal Investigator
Dates of funding: June 2009 – October 2011 (electively terminated June 2010 due to early graduation)
Funder: National Institute on Drug Abuse (F31 DA026689-01)

Educational Contributions

DIRECT TEACHING/PRECEPTING/SUPERVISING

Current courses

- EPID P8410: Psychiatric Epidemiology, 2016-2020
- EPIC Summer Institute: Principles of Epidemiology, 2014-2020
- EPID 787: Multi-level analysis for public health research, 2015-2020 (University of Michigan Graduate Summer Session in Epidemiology)

Former courses:
Role: Instructor

- EPIC Summer Institute: Multi-level analysis for public health research, 2016-2019

- HPMN P8545: Analysis of Large-Scale Data, 2016-2019
- Special short course: Multi-level analysis for public health research, 2017, (University of Cape Town, Cape Town, South Africa)
- EPID P6400: Principles of Epidemiology, 2010- 2015
- EPIC Summer Institute: Analysis of Complex Survey Data, 2011-2013
- MSPH Core: Quantitative Foundations of Public Health, 2012

Role: Assistant Course Director

- EPID P6400: Principles of Epidemiology, 2008, 2009

Role: Guest lecturer

- K Award Seminar Series, New York State Psychiatric Institute, 2013-2019
- EPID P9489: Advanced Techniques in Epidemiological Methods, 2017
- MPH Core Module 202-206: Principles of Epidemiology, (École des hautes études en santé publique, Paris, France), 2011-2016
- EPID P8416: Selected Problems in Measurement, 2010-2016
- EPID P8438: Design and Conduct of Observational Epidemiology, 2012-2015
- EPID P8419: Reading Seminar in Psychiatric Epidemiology, 2009-2015
- EPID P8470: Epidemiology of Alcohol and Drug Problems, 2011-2015
- EPID P9419: Master's Essay in Epidemiology, 2008-2015
- EPID P8471: Social Epidemiology, 2010

Role: Teaching assistant

- EPID P6400: Principles of Epidemiology, 2006-2008
- EPID P8421: Introduction to Clinical Psychiatry for Public Health, 2006
- EPID P8471: Social Epidemiology, 2008
- EPID P8419: Reading Seminar in Psychiatric Epidemiology, 2009
- EPID P8470: Epidemiology of Alcohol and Drug Problems, 2010

ADVISING AND MENTORSHIP

Master's students:

Mary Elizabeth Smith, 2011 (thesis, second reader)
Pedro Carneiro, 2012 (thesis, second reader)
Bryan Kutner, 2012 (thesis, second reader)
Erin Gilbert, 2012 (thesis, second reader)
Xinfan Liu, 2012 (thesis, second reader)
Charissa Pratt, 2013 (thesis, first reader)
Arti Virkud, 2013 (thesis, first reader)
Jonathan Platt, 2013 (thesis, first reader)
Edward Gastel, 2013 (thesis, first reader)
Nathalie DuRivage, 2013 (thesis, first reader)
Thomas Vo, 2014 (thesis, first reader)
Mark Morgan, 2014 (thesis, first reader)
Sabrina Cheng, 2014 (thesis, first reader)
Stephanie Brazis, 2014 (thesis, first reader)
Ruth Chang, 2014 (thesis, first reader)

Amy Lanza, 2015 (thesis, first reader)
David Sowa, 2015 (thesis, first reader)
Chidinma Egbukichi, 2015 (thesis, first reader)
Khudejha Asghar, 2015 (thesis, first reader)
Dahsan Gary, 2016 (thesis, first reader)
Joy Ukaigwe, 2016 (thesis, first reader)
Elizabeth Wartella, 2016 (thesis, first reader)
Rachel Webster, 2016 (thesis, first reader)
Caroline Hugh, 2017 (thesis, first reader)
Ghadah Gadi, 2017 (thesis, first reader)
Margaret Havunjian, 2018 (thesis, first reader)
Miriam Woodward, 2018 (thesis, first reader)
Ian Rodgers, 2018 (thesis, first reader)
Tatini Mal-Sarkar, expected 2019 (thesis, first reader)
* Sidney Kark Award for Excellence in Global Epidemiology
Noah Kreski, 2019 (thesis, first reader)
Mia Pandit, 2019 (thesis, first reader)
Catherine Gimbrone, 2019-present
* Abstract selected for oral presentation on Epi Masters Student Day

Doctoral students (former):
Joanne Brady, 2013-2014 (dissertation, second reader)
• Currently: senior research fellow, NORC at the University of Chicago
Melissa Dupont-Reyes, 2015-2017 (dissertation, second reader)
• Currently: Assistant Professor, University of Texas at Austin
Nina Banerjee, 2014-present (dissertation, second reader)
• Currently: psychologist in private practice, Orange County, CA
Julian Santaella, 2015-2018 (dissertation, sponsor)
• Currently: faculty, Universidad del Valle, Colombia
*Awarded the William Farr Award for Social Epidemiology for dissertation work, 2019
Jonathan Platt, 2015-2019 (dissertation, sponsor)
• Currently: post-doctoral scholar, Department of Epidemiology, Columbia University
*Awarded the William Farr Award for Social Epidemiology for dissertation work, 2019
Eleanor Hayes-Larson, 2018-2019
• Currently: post-doctoral scholar, Department of Epidemiology, University of California Los Angeles
* Awarded the Anna C. Gelman Award for Excellence in Epidemiology for dissertation work, 2019
Somjen Frazer, 2015-2019
- Currently: President and principal consultant, Strength in Numbers Consulting Group
Paula Bordelois, 2015-2019
Aravind Pillai, 2016-2020

Greg Cohen, 2018-present (dissertation, chair)
Currently: Post-doctoral research fellow, Boston University
Victor Puac-Polanco, 2018-present (dissertation, chair)
Post-doctoral research fellow, Harvard University

Doctoral students (present):
David Fink, 2015-present (dissertation, second reader)
Jonathan Pamplin, 2018-present (dissertation, chair)
Andrew Ratanatharathorn, 2018-present (dissertation, second reader)
Sarah McKetta, 2019-present (dissertation, sponsor)
Deborah Huang, 2019-present (dissertation, sponsor)
Michelle Nolan, 2019-present (dissertation, sponsor)
Alexandra Restrepo Henao, 2019-present (dissertation, sponsor)

Discussant for dissertation proposal defense:
Wendy Cheng, 2014
Kate Sapra, 2014
Emily Greene, 2016
Anton Plama, 2019
Adriana Maldonado, 2019

EDUCATIONAL ADMINISTRATION AND LEADERSHIP

- Director, Executive MS in Epidemiology Program, 2012-2015
  - Directly responsible for administration of the program, including designing the coursework and program, overseeing instructors, overseeing admissions process, advising students. Contact hours were 10 hours per seek.

TRAINING PROGRAM INVOLVEMENT

- T32 MH013043-45 "A Research Training Program in Psychiatric Epidemiology"
  Role: Co-Director (with Ezra Susser, Bruce Dohrenwend, and Sharon Schwartz)
- T32 DA-031099-05 "Epidemiology of Substance Use Disorders Training Program at Columbia University" (PI: Hasin)
  Role: Faculty, Steering Committee
- T32 ES023772-02 "Training Program in Environmental Life Course Epidemiology" (PI: Factor-Litvak
  Role: Faculty

Publications

PEER-REVIEWED RESEARCH PUBLICATIONS IN PRINT OR OTHER MEDIA

\+ **mentee**
*** senior author**

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9. **Keyes KM**, Davey Smith G, Susser E. (2013). On sibling designs. Epidemiology, 24(3): 473-4. PMID: 23549193.
10. **Keyes KM**, Cerda M. (2013). Racial/ethnic differences in alcohol-related suicide: A call for focus on unraveling paradoxes and understanding structural forces that shape alcohol-related health. Alcoholism: Clinical and Experimental Research, ePub Feb 26. PMID: 23441581. PMCID: PMC5540371.
11. Wall MM, Poh E, Cerda M, **Keyes KM**, Galea S, Hasin DS. (2012). Commentary on Harper S, Strumph EC, Kaufman JS. Do Medical Marijuana Laws Increase Marijuana Use? Replication Study and Extension. Annals of Epidemiology, 22(7): 536-7. PMID: 22534177. PMCID: PMC3547124.
12. Kirkbride JB, **Keyes KM**, Susser E. 2018. City Living and Psychotic Disorders-Implications of Global Heterogeneity for Theory Development. JAMA Psychiatry, ePub Oct 10th. PMID: 30304485.
13. Susser E, **Keyes KM**, Mascayano F. 2018. Health pregnancy and prevention of psychosis. World Psychiatry, 17(3):357-358. PMID: 30192106.
14. **Keyes KM**. 2018. Invited commentary: Marijuana, drug use, and mental health in the United States: a tale of two generations. Addiction, 113(3):482-483. PMID: 29423983.
15. **Keyes KM**, Tracy M, Mooney SJ, Shev A, Cerda M. 2017. Invited commentary: Agent-based models: bias in the face of discovery. American Journal of Epidemiology, ePub June 30. PMID: 28673036. PMCID: PMC5860003.

16. **Keyes KM**, Susser E. 2017. Invited commentary: An ingenious approach to examining the relationship between maternal stress and offspring health? American Journal of Epidemiology, Feb 3, 1-4. PMID: 28158433.
17. Susser E, **Keyes KM**. 2017. Prenatal nutritional deficiency and psychosis: where do we go from here? JAMA Psychiatry, Feb 22. PMID: 28241254. PMCID: PMC5488265.
18. Susser E, Verhulst S, Kark JD, Factor-Litvak PR, **Keyes K**, Magnus P, Aviv A. 2016. Non-Dynamic Association of Depressive and Anxiety Disorders with Leukocyte Telomere Length? American Journal of Psychiatry, 173(11): 1147. PMID: 27798991. PMCID: PMC5325116.
19. Reininghaus U, **Keyes KM**, Morgan C. Novel methods in psychiatric epidemiology. 2016. Soc Psychiatry and Psychiatr Epidemiol. ePub Jun 22. PMID: 27333982. PMCID: PMC4962869.
20. **Keyes KM**, Barnes D, Bates L. 2015. A letter in response to: Weaver A, Himle JA, Taylor RJ, Matusko NN, Abelson JM. Urban vs Rural Residence and the Prevalence of Depression and Mood Disorder Among African American Women and Non-Hispanic White Women. JAMA Psychiatry. PMID: 26561032. PMCID: PMC4671197.
21. **Keyes KM**, Susser E, Cheslack-Postava K, Fountain C, Liu K, Bearman PS. 2014. Authors' response: Cohort effects explain the increase in autism diagnosis: an identifiability problem of the age-period-cohort model. International Journal of Epidemiology, 43(5): 1381-8. PMID: 25393200. PMCID: PMC4265900.
22. Bates L, Barnes D, **Keyes KM**. 2011. Re: Reconsidering the role of social disadvantage in physical and mental health: stressful life events, health behaviors, race, and depression. American Journal of Epidemiology. PMID: 21540321. PMCID: PMC3937594.

THESIS

Keyes, KM. Ecologic-level disapproval and the prevalence of substance use: A multi-level age-period-cohort analysis of high-school attending adolescents in the United States. Columbia University, 2010.

OTHER NON-PEER REVIEWED PUBLICATIONS IN PRINT OR OTHER MEDIA

Teutsch SM, Geller A, Negussie Y, eds. Getting to Zero Alcohol-Impaired Driving Fatalities: A Comprehensive Approach to a Persistent Problem. National Academicies of Sciences, Engineering, and Medicine. Washington, DC; 2018.

- Committee member for consensus study, 2017-2018

Invited and/or Peer-Selected Presentations at Regional, National or International Levels

CONFERENCE PRESENTATIONS
REGIONAL

1. Changes in United States health policy: implications for substance use and injury. Society for Epidemiological Research, symposium chair, June 2018, Baltimore, MD.
2. Consequences of medical and recreational cannabis legislation on opioid-related harm. Society for Epidemiological Research, symposium presentation, June 2018, Baltimore, MD.
3. Are urban and rural health differences due to exposure prevalence variation or interaction: when and why does it matter? Society for Epidemiological Research, symposium presentation, June 2018, Baltimore, MD
4. Who thinks like that? Survey methods for non-survey data. Society for Epidemiological Research, symposium presentation, June 2018, Baltimore, MD.
5. The Great Sleep Recession: Changes in Sleep Duration Among US Adolescents, 1991-2012. Symposium presentation, Society for Research on Child Development. March 2015, Philadelphia, PA.
6. Has the population prevalence of adolescent sensation seeking and its relation to substance use changed over time? Symposium presentation, Society for Research on Child Development. March 2015, Philadelphia, PA.
7. Understanding substance use epidemiology across time, space, and generation. Society for Epidemiologic Research, Symposium chair, June 2013, Boston, MA.
8. Early life stress and adult psychiatric disorders: assessing causation in a sea of correlation. Society for Epidemiologic Research, Symposium presentation, June 2013, Boston, MA.
9. Racial/ethnic differences in alcohol-attributable homicide: how do we move forward? Society for Epidemiologic Research, Symposium presentation, June 2013, Boston, MA.
10. New Methods for an Old Epidemiologic Problem: Age, Period, and Cohort Effects. Society for Epidemiologic Research, Symposium chair, June 2013, Boston, MA.
11. Testing the 'Jackson hypothesis': are black/white differences in depression due to differential effects of stress and unhealthy behaviors? Symposium presentation, Psychiatric Epidemiology Faculty/Fellows Training Seminar. November 2010, New York, NY.
12. Adverse childhood events and the structure of common psychiatric disorders. Symposium presentation, Adverse Childhood Experiences, Personality Psychopathology, and Alcohol Disorders. May 2010, New York, NY.
13. The role of craving in future classifications of alcohol use disorders. Symposium presentation, Adverse Childhood Experiences, Personality Psychopathology, and Alcohol Disorders. December 2009, New York, NY.
14. 'Age Selection of Mortality from Tuberculosis': a re-analysis of Frost on the 70th anniversary of publication. Symposium presentation, American Public Health Association, November 2009, Philadelphia, PA.
15. Population-level disapproval and the prevalence of substance use: a multi-level age-period-cohort analysis of high-school attending adolescents in the United States, 1976-2008. Symposium presentation, Research Seminars in Epidemiology, October 2009, New York, NY.

16. Age-Period-Cohort estimation throughout history: tracing the meaning of a 'cohort effect' Symposium presentation. Psychiatric Epidemiology Faculty/Fellows Training Seminar. February 2009, New York, NY.
17. Influence of a drinking quantity and frequency measure on the prevalence and demographic correlates of DSM-IV alcohol use disorders. Symposium presentation, Research Society on Alcoholism. June 2008, Washington, DC.
18. Methodological Issues in the Estimation of Age-Period-Cohort Effects. Symposium presentation. Psychiatric Epidemiology Faculty/Fellows Training Seminar. March 2008, New York, NY.
19. Disentangling age-period-cohort effects: problems and possibilities. Symposium presentation, American Psychopathological Association. March 2008, New York, NY.
20. Time in the causal landscape: age, period, and cohort effects in alcohol and drug epidemiology. Symposium presentation, Psychiatric Epidemiology Faculty/Fellow Training Seminar. May 2007, New York, NY.
21. Birth cohort effects on gender differences in the risk for alcohol and drug dependence. Symposium presentation, Research Society on Alcoholism. June 2006, Baltimore, MD.
22. Gender differences in the risk for alcohol abuse and dependence: the effect of birth cohort. Symposium presentation, Psychiatric Epidemiology Faculty/Fellow Training Seminar. December 2005, New York, NY.
23. Cannabis withdrawal in 2,613 lifetime heavy cannabis users. Symposium presentation, Novel Phenotype Development for Genetics Studies of Substance Abuse Disorders. September 2005, New York, NY.

NATIONAL

1. Family matters: using family designs to control confounding in observational studies. Society for Epidemiologic Research, symposium chair, June 2019, Minneapolis, MN.
2. Simulating firearm suicide based on gun ownership disqualifications: an agent-based modeling approach. Association for Psychological Science, symposium presentation, May 2019, Washington, DC.
3. Rapid increases in depressive symptoms among US adolescents: 1991-2018. Society for the Advancement of Violence and Injury Research, symposium presentation, April 2019, Cincinnati, OH.
4. Declines in the relationship between adolescent depressive affect and binge drinking: implications for public mental health. Research Society on Alcoholism, symposium presentation, June 2018, San Diego, CA.
5. Psychiatric epidemiology in the era of precision medicine: what is our role? Symposium chair, Society for Epidemiologic Research, June 2017, Seattle, WA.
6. Fifty years of high impact epidemiological research on drug use disorders and related conditions: Looking back and ahead. Symposium presentation, Society for Epidemiologic Research, June 2017, Seattle, WA.
7. Agent-based model of alcohol taxation effects on violence and homicide in New York City. Symposium presentation, Research Society on Alcoholism, June 2016, New Orleans, LA.

8. The impact of traumatic experiences across diverse populations: causes, consequences, and correlates. Symposium chair, Society for Epidemiologic Research, June 2016, Miami, FL.
9. Agent-Based models and the G-Formula: Comparable Approaches for Evaluating Population Intervention Effects? Symposium discussant, Society for Epidemiologic Research, June 2016, Miami, FL.
10. How similar are survey respondents to the general population? Symposium presentation, Society for Epidemiologic Research, June 2016, Miami, FL.
11. Mental Health and Aging: Chronic Disease, Cognition, and Pathways Connecting Mind and Body. Symposium chair, Society for Epidemiological Research, June 2015, Denver, CO.
12. Teaching epidemiology by building on foundational concepts. Symposium presentation, Society for Epidemiological Research, June 2015, Denver, CO.
13. The mathematical limits of genetic prediction for complex chronic disease. Symposium presentation, Society for Epidemiological Research, June 2015, Denver, CO.
14. Alcohol Interventions and Rates of Violence and Homicide in New York City: an Agent-Based Approach. Symposium presentation, Society for Epidemiological Research, June 2015, Denver, CO.
15. Racial/ethnic differences in alcohol use across the life course: an explanation of health disparities? International Epidemiological Association, August 2014, Anchorage, AL.
16. Health within and across generations: new research in life course epidemiology. Symposium chair, Society for Epidemiologic Research, June 2014, Seattle, WA.
17. How should we prioritize 'external validity' when aiming to conduct an epidemiology that matters? Symposium presentation, Society for Epidemiologic Research, June 2014, Seattle, WA.
18. Multi-national birth cohort trends in sensation seeking in the United States from 1976 to 2011. Symposium presentation, Society for Research on Adolescents, March 2014, Austin, TX.
19. Racial/ethnic differences in drinking in the US: paradoxes, problems, and research priorities. Research Society on Alcoholism, Symposium chair and presentation, June 2013, Orlando, FL.
20. The burden of loss: unexpected death and psychiatric disorders across the life course. International Society for Traumatic Stress Studies, Symposium presentation, November 2012, Los Angeles, CA.
21. The social norms of birth cohorts: age, period, and cohort effects in adolescent and adult binge drinking. Symposium presentation, Society for Research on Child Development, October 2012, Tampa, FL.
22. Thought disorders in the meta-structure of psychopathology. Symposium presentation, Research Society on Alcoholism, June 2012, San Francisco, CA.
23. Time Trends and Their Explanations. Symposium chair, Research Society on Alcoholism, June 2011, Atlanta, Georgia.
24. Novel Methods to Assess Societal-Level Causes of Alcohol Disorders Across Time and Place. Symposium chair, Research Society on Alcoholism, June 2010, San Antonio, Texas.

25. A multi-level framework for understanding birth cohort effects. Symposium presentation, Research Society on Alcoholism, June 2010, San Antonio, Texas.
26. A Comprehensive Approach to Age-Period-Cohort Analysis. Plenary session presentation, Society for Epidemiologic Research. June 2008, Chicago, IL.
27. Economic capital and problem alcohol use: the positive relationship between income and the DSM-IV alcohol abuse diagnosis. Symposium presentation, Research Society on Alcoholism, July 2007, Chicago, IL.
28. Keyes KM, Hasin DS. Birth cohort effects on gender differences in the risk for drug dependence. College on Problems of Drug Dependence. July 2006, Scottsdale, AZ.
    * Selected for Women & Gender Junior Investigator Award

INTERNATIONAL

1. Mental health and firearm violence: what role should disqualification criteria on firearm ownership play? Symposium presentation International Federation of Psychiatric Epidemiology, October 2017, Melbourne, Australia.
2. Mental health and firearm violence: Understanding social and environmental contexts on the path to prevention. Symposium chair, International Federation of Psychiatric Epidemiology, October 2017, Melbourne, Australia.
3. Transdiagnostic psychiatric disorder risk associated with early and late age of menarche: a latent modeling approach. Symposium presentation, International Federation of Psychiatric Epidemiology, October 2017, Melbourne, Australia.
4. Utilising epidemiology to guide innovative prevention for comorbid mental and substance use problems in young people. Symposium discussant, International Federation of Psychiatric Epidemiology, October 2017, Melbourne, Australia.
5. The influence of medical marijuana laws on adolescent and adult outcomes: current state evidence from the United States. Symposium presentation, World Psychiatric Association, October 2017, Berlin, Germany.
6. How healthy are survey respondents compared to the general population? A comparison of mortality rates from linked death records. Symposium presentation, World Psychiatric Association Epidemiology Section, April 2016, Munich, Germany.
7. Anxious and angry: course and comorbidity of intermittent explosive disorder and anxiety disorders in adolescence. Symposium presentation, International Federation of Psychiatric Epidemiology, October 2015, Bergen, Norway.
8. Trajectories of alcohol and cigarette use across the lifecourse: evidence from a pregnancy cohort. Symposium presentation, World Psychiatric Association, September 2014, Madrid, Spain.
9. Maternal alcohol consumption and offspring psychopathology. European Public Health Association Conference, Symposium presentation, November 2013, Brussels, Belgium.
10. Understanding the teenage brain in context: 35 years of adolescent sensation seeking in the United States. International Federation of Psychiatric Epidemiology, Symposium chair and presentation, June 2013, Leipzig, Germany.
11. Comorbidity of less common psychiatric disorders in the meta-structure of psychopathology. Symposium presentation, World Psychiatric Association, October 2012, Prague, Czech Republic.

12. How can thought disorders be conceptualized in the meta-structure of psychopathology? Symposium presentation, Life History Society, October 2012, Surrey, England.
13. Understanding family-based designs using Directed Acyclic Graphs. Symposium presentation, World Psychiatric Association Epidemiology Section, March 2012, Sao Paulo, Brazil.
14. Childhood Maltreatment and the Structure of Common Psychiatric Disorders. Symposium presentation, Society for Epidemiologic Research, June 2011, Montreal, Canada.
15. Methodological issues in the assessment of adverse childhood events. Symposium chair, Society for Epidemiologic Research, June 2011, Montreal, Canada.
16. Time as a multi-level risk factor: the impact of time period- and birth cohort-specific social norms on adolescent marijuana use, 1976-2007. Symposium presentation, École Des Hautes Études En Santé Publique, January 2010, Paris, France.
17. Challenging the paradigm of a "telescoping" phenomenon in gender differences for substance disorders: results of a cohort analysis in the U.S. population. Symposium presentation, International Federation of Psychiatric Epidemiology. April 2009, Vienna, Austria.

INVITED LECTURES

REGIONAL

1. Using agent-based models to simulate the opioid epidemic: a critical review of the literature and proposed framework for New York State and beyond. HIV Intervention Science Training Program for Underrepresented New Investigators. August 2019, New York, NY.
2. Depression's got a hold of me: Gender differences and generational trends in alcohol use and mental health among US adolescents and adults. Epidemiology seminar, University of Pittsburgh School of Public Health, February 2019, Pittsburgh, PA.
3. Depression's got a hold of me: Gender differences and generational trends in alcohol use and mental health among US adolescents and adults. Substance Abuse Epidemiology Training Program seminar, Columbia University, October 2018, New York, NY.
4. Adolescent mental health and substance use in the 21st century: implications for research and prevention. NIAAA Webinar: Women, Drinking, and Pregnancy Working group. November 2018, Bethesda, MD.
5. Depression's got a hold of me: Gender differences and generational trends in alcohol use and mental health among US adolescents and adults. Substance Abuse Epidemiology Training Program seminar, Columbia University, October 2018, New York, NY.
6. Depression's got a hold of me: Gender differences and generational trends in alcohol use and mental health among US adolescents and adults. Epidemiology and Biostatistics Seminar, Drexel University, November 2018, Philadelphia, PA.

7. Mental health over the life course: adolescence. National Academy of Sciences workshop: Women's Mental Health across the Life Course. March 7th, 2018. Washington DC.
8. Life Course Psychopathology: The Next Decade. American Psychopathological Association, invited talk, March 3rd, 2018. New York, NY.
9. As adolescent substance use declines, depression and suicidality increase: a tale across generations. NYU Population Health, Epidemiology Seminar Series. December 4th, 2017, New York, NY.
10. Historical and current trends in adolescent heavy alcohol use, depressive affect, and their relationship: implications for adolescent suicide in the United States. NIAAA Workshop to Explore Research Needs in Addressing Alcohol-Related Suicide, September 2017, National Institute of Alcohol Abuse and Alcoholism, Rockville, Maryland.
11. Alcohol use and morbidity across historical time: what does variation tell us about environmental determinants of alcohol-related outcomes? National Institute of Health Director's Wednesday Afternoon Lecture Series (WALS), May 2017, NIH, Bethesda, MD.
12. The role of epidemiology in population mental health in the 21st century: history, current progress, future directions. Population Health Research Seminar, October 2016, New York University, New York, NY.
13. How and why do psychiatric disorders change across time. Brain Health Colloquium, Harvard T.H. Chan School of Public Health, Seminar presentation, April 2016, Boston, MA.
14. The mathematical limits of genetic prediction for complex chronic disease. Symposium presentation, American Psychopathological Association, March 2016, New York, NY.
15. How and why do psychiatric disorders change across time. Institute for Translational Epidemiology, Mount Sinai School of Medicine, Seminar presentation, January 2016, New York, NY.
16. Psychiatric disorders among bereaved individuals. Grand Rounds speaker, Hartford Hospital Institute of Living, October 2014, Hartford, CT.
17. How can we intervene in neighborhoods to reduce racial/ethnic inequalities in alcohol-related homicide? Simulating in-silico counterfactuals. Partnership for a Healthier New York City, June 2014, New York, NY.
18. How can we intervene in neighborhoods to reduce racial/ethnic inequalities in alcohol-related homicide? Simulating in-silico counterfactuals. Innovations in Translating Injury Research Into Effective Prevention, May 2014, New York, NY.
19. Social norms, attitudes, and behavior: how do we harness intention for public health prevention? Columbia University Epidemiologic Science Symposium, April 2014, New York, NY
20. Age, period, and cohort effects: an introduction to theory and approaches to analysis. CUNY School of Public Health Epidemiology and Biostatistics Seminar Series, Invited lecture, November 2013, New York, NY.
21. Social norms and alcohol use: evidence and recommendations for New York City. Community Services Board Meeting, Invited lecture, New York City Department of Health, March 2013, New York, NY.

22. How does exogenous and endogenous hormone variation affect mental health? New designs for old problems. Psychiatric-Neurological Epidemiology Cluster Seminar, Invited lecture, Columbia University, February 2013, New York, NY.
23. The critical role of social norms in population health. Symposium presentation, Columbia University Epidemiology Scientific Symposium: Charting the Course of Social Epidemiology in the Next 25 Years, Symposium presentation, October 2012, New York, NY.
24. Time trends in alcohol use: Understanding cohort effects, Adult Psychiatry Grand Rounds, Columbia University Department of Psychiatry, May 2012, New York, NY.
25. The Epidemiology of Substance Use Disorders. Sexuality and HIV Seminar, HIV Center for Clinical and Behavioral Science. February 2011, New York, NY

NATIONAL

1. The Rapid Decline in Adolescent Mental Health in the 21st Century: Magnitude, Causes, and Public Health Implications. Dean's Seminar Series, College of Health and Human Services, George Mason University, January 2020.
2. The changing landscape of adolescent mental health and substance use in the 21st century. Epidemiology seminar, National Institute on Drug Abuse, March 2019, Bethesda, MD.
3. Depression's got a hold of me: Gender differences and generational trends in alcohol use and mental health among US adolescents and adults. Epidemiology seminar, Michigan State University, March 2019, Lansing, MI.
4. Psychiatric Disorders after Loss. Dean's Symposium on Death and Dying, Boston University School of Public Health, February 2019, Boston, MA.
5. Does epidemiology matter? Epidemiology and population health science in the 21st century. Johns Hopkins School of Public Health, Epidemiology Centennial Symposium, November 2018, Baltimore, MD.
6. Opioid use, disorder, and mortality: past, present, and evidence-based control strategies. Mass Torts Made Perfect conference, invited talk, April 2018, Las Vegas, NV.
7. The epidemiology of opioid use, opioid disorder, and overdose in the United States: past, present, and evidence-based control strategies. Keynote address, Kentucky Association of Counties annual conference, November 2017, Louisville, Kentucky.
8. Fundamentals of age-period-cohort analysis. Epidemiology Seminar Series, February 2017, University of California San Francisco, San Francisco, California.
9. The role of epidemiology in population mental health in the 21st century: history, current progress, future directions. Epidemiology Seminar Series, November 2016, Virginia Commonwealth University, Richmond, Virginia.
10. Alcohol use and morbidity across historical time: what does variation tell us about environmental determinants of alcohol-related outcomes? Plenary talk, Research Society on Alcoholism, June 2016, New Orleans, LA.
11. Using complex systems modeling to examine alcohol-attributable homicide in New York City. Invited lecture, Injury Prevention Research Center, Office of the Vice-Chancellor for Research, Social Epidemiology Program, Epidemiology Department,

Gillings School of Global Public Health, University of North Carolina. October 2015, Chapel Hill, NC.

12. Racial/ethnic differences in substance use across the life course. Grand Rounds speaker, Alcohol Research Group. November 2014, Berkeley, California.
13. A brief introduction to age-period-cohort methodology. SER Experts presentation, Society for Epidemiologic Research, June 2014, Seattle, WA.
14. Time in the causal landscape: problems and possibilities in age-period-cohort research. Survey Research Center, February 2010, Ann Arbor, Michigan.

INTERNATIONAL

1. Does epidemiology matter? Epidemiology and population health science in the 21st century. University College London Department of Psychiatry, April 2019, London, England.
2. How health disparities are obscured and underreported in national survey data, and implications for policy. University of Glasgow, April 2019, Glasgow, Scotland.
3. Depression's got a hold of me: Gender differences and generational trends in alcohol use and mental health among US adolescents and adults. Centro de Investigación en Sociedad y Salud, Universidad Mayor, November 2018, Santiago, Chile.
4. The role of epidemiology in population mental health in the 21st century: history, current progress, future directions. Seminar Series, April 2017, French National Institute of Health and Medical Research (INSERM), Paris, France.
5. The role of epidemiology in population mental health in the 21st century: history, current progress, future directions. Seminar Series, August 2017, National Institute of Occupational Health, Oslo, Norway.
6. The role of epidemiology in population mental health in the 21st century: history, current progress, future directions. Key note address, Epidemiology Student Research Day, April 2017, McGill University, Montreal, Canada.
7. The role of epidemiology in population mental health in the 21st century: history, current progress, future directions. Epidemiology Seminar Series, April 2017, University of Capetown, Capetown, South Africa.
8. Why does epidemiology matter? Invited lecture, International Journal of Epidemiology Conference, October 2016, Bristol, UK.
9. Cohort studies in epidemiology: considering cross-generational influences on health. Invited speaker, World Psychiatric Association Epidemiology Section, April 2016, Munich, Germany.
10. How and why do psychiatric disorders change across time. Canadian Association of Psychiatric Epidemiology, Keynote speaker, September 2015, Vancouver, Canada.
11. Advances in age, period, and cohort effect analysis. Faculty of Health Sciences Research Seminar Series, Invited lecture, September 2015, Vancouver, Canada.
12. The burden of loss: unexpected death and psychiatric disorders across the life course. Symposium presentation, World Psychiatric Association Epidemiology Section, October 2014, Nara, Japan.
13. Age, period, and cohort effects: an introduction to theory and approaches to analysis. University of Manitoba Clinical Health Sciences, Department of Psychiatry, Invited lecture, January 2013, Winnipeg, Canada.

Katherine Keyes, PhD Expert Report

Case No. 1:17-op-45053-DAP and No. 1:17-op-45054 Opioid Litigation

EXHIBIT B

Materials Considered

MATERIALS CONSIDERED

1. Aaron M. Gilson, Karen M. Ryan, David E. Joranson, and June L. Dahl. A Reassessment of Trends in the Medical Use and Abuse of Opioid Analgesics and Implications for Diversion Control: 1997–2002. Journal of Pain and Symptom Management Vol. 28 No. 2

2. Adams EH, Breiner S, Cicero TJ, et al. A comparison of the abuse liability of tramadol, NSAIDs, and hydrocodone in patients with chronic pain. J Pain Symptom Manage. 2006;31(5):465-476. doi:10.1016/j.jpainsymman.2005.10.006

3. Adoption & Foster Care Statistics. Children's Bureau: An Office of the Administration for Children & Families. https://www.acf.hhs.gov/cb/research-data- technology/statistics-research/afcars.

4. Ahmad F, Rossen L, Sutton P. Provisional drug overdose death counts. Natl Cent Heal Stat. 2020. https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm.

5. Ahn R, Woodbridge A, Abraham A, et al. Financial ties of principal investigators and randomized controlled trial outcomes: cross sectional study. BMJ. 2017;356:i6770. doi:10.1136/bmj.i6770

6. Albizu-Garcia CE, Caraballo JN, Caraballo-Correa G, Hernandez-Viver A, Roman-Badenas L. Assessing need for medication-assisted treatment for opiate-dependent prison inmates. Subst Abus. 2012;33(1):60-69. doi:10.1080/08897077.2011.620462

7. Aleksandra Zgierska, Michael Miller, and David Rabago. Patient Satisfaction, Prescription Drug Abuse, and Potential Unintended Consequences. JAMA Vol 307, No. 13

8. Allen, N. et al. Non-Pharmacological interventions for Neonatal Abstinence Syndrome. Addiction, 113, 1750–1752

9. Allen, S. et al. Correlates of Transactional Sex Among a Rural Population of People Who Inject Drugs. AIDS Behav. 2020 Mar;24(3):775-781

10. Allen, S. et al. Estimating the Number of People Who Inject Drugs in A Rural County in Appalachia. Am J Public Health. 2019;109:445–450

11. Allen, S. et al. Take-home naloxone possession among people who inject drugs in rural West Virginia. Drug and Alcohol Dependence Volume 204, 1 November 2019, 107581

12. Allison L. Pitt, Keith Humphreys, Margaret L. Brandeau. Modeling Health Benefits and Harms of Public Policy Responses to the US Opioid Epidemic. Department of Management Science and Engineering, Stanford University, Stanford, CA; Center for Innovation to Implementation, VA Palo Alto Health Care System, Palo Alto, CA; Department of Psychiatry and Behavioral Sciences, Stanford University, Stanford, CA

13. Alpert A, Powell D, Pacula RL. Supply-side drug policy in the presence of substitutes: evidence from the introduction of abuse-deterrent opioids. Am Econ J Econ Policy. 2018;10(3):1-35.

14. Altarac M, Saroha E. Lifetime prevalence of learning disability among US children. Pediatrics. 2007;119 (Supplement 1):S77 LP-S83. doi:10.1542/peds.2006-2089L

15. American College of Obstetricians and Gynecologists. Opioid use and opioid use disorder in pregnancy. Committee opinion No. 711. Obstet Gynecol. 2017; 130:e81-e94.

16. American Psychiatric Association (2000). Diagnostic and statistical manual of mental disorders (4th ed., Text Revision)

17. AMFAR. Opioid & Health Indicators Database. WV Opioid Epidemic. https://opioid.amfar.org/WV

18. Amlani A, McKee G, Khamis N, Raghukumar G, Tsang E, Buxton JA. Why the FUSS (Fentanyl Urine Screen Study)? A cross-sectional survey to characterize an emerging threat to people who use drugs in British Columbia, Canada. Harm Reduct J. 2015;12:54. doi:10.1186/s12954-015-0088-4

19. Anderson P, Chisholm D, Fuhr DC. Effectiveness and cost-effectiveness of policies and programmes to reduce the harm caused by alcohol. Lancet. 2009;373(9682):2234- 2246. doi:10.1016/S0140- 6736(09)60744-3

20. Anderson VC, Burchiel KJ. A prospective study of long-term intrathecal morphine in the management of chronic nonmalignant pain. Neurosurgery. 1999;44(2):281-289.

21. Andrew Kolodny, David T. Courtwright, Catherine S. Hwang, Peter Kreiner, John L. Eadie, Thomas W. Clark, and G. Caleb Alexander. The Prescription Opioid and Heroin Crisis: A Public Health Approach to an Epidemic of Addiction. Annu. Rev. Public Health 2015 . 36:559–74

22. Andrews L, Davies TH, Linz M and Payne M. Polydrug Abuse and Fetal Exposure: A Review. J Pediatr & Child Health Care. 2018; 3(1): 1019

23. Andrews, L. et al. Necrotizing enterocolitis and its association with the neonatal abstinence syndrome. Journal of Neonatal-Perinatal Medicine 13 (2020) 81–85

24. Aron J. Hall, Joseph E. Logan, Robin L. Toblin, James A. Kaplan, James C. Kraner, Danae Bixler, Alex E. Crosby, Leonard J. Paulozzi. Patterns of Abuse Among Unintentional Pharmaceutical Overdose Fatalities. JAMA Vol. 300, No. 22

25. Art Van Zee. The Promotion and Marketing of OxyContin: Commercial Triumph, Public Health Tragedy. American Journal of Public Health

26. ASPPH Report and Recommendation from the ASPPH Bringing Science to Bear on Opioids: Task Force on Public Health Initiatives to Address the Opioid Crisis November 2019

27. Assurance of Discontinuance Pursuant to Exec Law §63(15)

28. Atluri S, Sudarshan G, Manchikanti L. Assessment of the trends in medical use and misuse of opioid analgesics from 2004 to 2011. Pain Physician. 2014;17(2):E119-28.

29. Attila Mihalik. A Call to Action: America's Painful Addiction. Inside Pain Management Vol 3, No. 3

30. Attorney General Patrick Morrisey. DEA's failure to combat diversion cost lives: Results from the West Virginia Attorney General's investigation into the DEA's catastrophic failure to manage the National Drug Quota System from 2010-2016. 2020.

31. Babcok, C. Bringing Naloxone to Ground Zero: Huntington, WV. Journal of the American Pharmacists Association 57 (2017) S8eS11

32. Babor T. Alcohol: No Ordinary Commodity: Research and Public Policy. Oxford University Press; 2010.

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126. Communication with Ellen A. Thompson, MD - Professor, Marshall Health, Huntington, West Virginia

127. Communication with Gordon Merry - Cabell County EMS Director

128. Communication with Hank Dial - City of Huntington Police Chief

129. Communication with Jan Rader - City of Huntington Fire Chief

130. Communication with Keith Thomas - Coordinator of Student Support, Cabell County Schools

131. Communication with Kelly Watts - Assistant Superintendent, Division of Instruction and Leadership, Cabell County Schools

132. Communication with Lyn O'Connell, PhD - Associate Director of Addiction Sciences, Marshall Health

133. Communication with Marcia Knight - Director of Education, Cabell County EMS

134. Communication with Michael Kilkenny, MD - Director, Cabell County Department of Public Health

135. Communication with Ray Cornwell - City of Huntington Police Captain

136. Communication with Rocky Johnson - City of Huntington Police Department, Police Captain, Special Investigations Bureau (Former)

137. Communication with Sean Loudin, MD – Associate Professor, Marshall University School of Medicine

138. Communication with Stephen Petrany, MD - Chair of Family & Community Health, Marshall University School of Medicine

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DEPOSITION

795. Deposition Transcript and Exhibits of Craig Preece

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797. Deposition Transcript and Exhibits of Carney

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803. Deposition Transcript and Exhibits of Lisa Kohler

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808. Deposition Transcript and Exhibits of Zimmerman

809. Deposition Transcript and Exhibits of Beth Thompson

810. Deposition Transcript and Exhibits of Charles (Chuck) Zerkle

811. Deposition Transcript and Exhibits of Crystal Welch

812. Deposition Transcript and Exhibits of Deron Runyon

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824. Deposition Transcript and Exhibits of Paul Hunter
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826. Deposition Transcript and Exhibits of Ray Canafax
827. Deposition Transcript and Exhibits of Rocky Johnson
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831. Deposition Transcript and Exhibits of Sue Ann Painter
832. Deposition Transcript and Exhibits of Tim Hazelett
833. Deposition Transcript and Exhibits of Tom McComas
834. Deposition Transcript and Exhibits of Vic Brown, Appalachia HIDTA
835. Excerpts of Bruce Gundy Deposition Testimony
836. Excerpts of Nathan Hartle Deposition Testimony Volume 1
837. Excerpts of Joseph Natko Deposition Testimony
838. Excerpts of Raymond Carney Deposition Testimony
839. Excerpts of Sharon Hartman Deposition Testimony
840. Rough Deposition Transcript of T. Davies

All Expert Witness reports and supplements from MDL 2804 served on March 25, 2019 and May 10, 2019 as well as materials identified within.

All Expert Witness reports from the NY Opioid Litigation 400000/2017 served on December 19, 2019 and February 3rd, 2020 as well as materials identified within.

All Expert Witness reports from Cabell County Commission and City of Huntington, West Virginia, (The Cabell Huntington Community) v. AmerisourceBergen Drug Corporation, Cardinal Health, Inc., and McKesson Corporation served on August 3, 2020 as well as materials identified within.

All items referenced in Dr. Keyes's expert witness reports or listed on Materials Considered lists.

Katherine Keyes, PhD Expert Report

Case No. 1:17-op-45053-DAP and No. 1:17-op-45054 Opioid Litigation

EXHIBIT C

Compensation

Katherine M. Keyes, PhD
Department of Epidemiology
Columbia University
722 West 168th Street
New York, NY 10032
(212) 305-6706
kmk2104@columbia.edu

Compensation
Reviewing materials and writing report: $400 per hour
Deposition and trial testimony: $550 per hour

Katherine Keyes, PhD Expert Report

Case No. 1:17-op-45053-DAP and No. 1:17-op-45054 Opioid Litigation

EXHIBIT D

Prior Testimony

Katherine M. Keyes, PhD
Department of Epidemiology
Columbia University
722 West 168th Street
New York, NY 10032
(212) 305-6706
kmk2104@columbia.edu

Prior Testimony

1. *National Prescription Opiate Litigation*, MDL No. 2804 (N.D. Ohio, Case 1:17-md-2804)

2. *In Re Opioid Litigation*, (Suffolk County, New York Supreme Court, Index No. 400000/2017), relating to Case Nos. County of Suffolk, 400001/2017; County of Nassau, 400008/2017; and New York State, 400016/2018

Katherine Keyes, PhD Expert Report

Case No. 1:17-op-45053-DAP and No. 1:17-op-45054 Opioid Litigation

EXHIBIT E

Publications

Katherine M. Keyes, PhD
Department of Epidemiology
Columbia University
722 West 168th Street
New York, NY 10032
(212) 305-6706
kmk2104@columbia.edu

Publications

Please refer back to Exhibit A: Keyes CV for a list of publications.